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THE END OF THE WAR WITH GERMANY AND AFTERWARDS.

As this issue is in the press the end of the war with Germany has been announced. Australia stands with bowed head in thankfulness for the success of Allied arms, in honour of those who have given their lives, remembering the captive, the wounded and the bereaved and with a resolve to complete the task that remains. Australian medicine has been charged with the care of the men and women of His Majesty's Australian Forces and of those working at home. This work will go on until the remaining enemy is vanquished. And afterwards Australian doctors will join their countrymen in the rebuilding of national life, having as their special care the broken in body and mind.

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RAT LEPROSY: OBSERVATIONS AND TRANSMISSION.

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IN 1903 Stefansky observed at Odessa a leprosy-like disease in *Rattus norvegicus* due to acid-fast mycobacteria. Owing to the similarity to human leprosy, the life history of this rat organism has been closely studied in an endeavour to throw some light on the human condition. Morphologically the human and rat leprosy organisms appear to be similar, and they produce a similar reaction when transmitted to certain animals. Salle (1934) and other workers are convinced of their affinity. Experimental evidence here appears to confirm this attitude. Recently, Francis (1943) indicated an affinity between the leprous disease and Johne's bovine disease.

McKinley (1939) objects to the name "rat leprosy". The similarity between the superficial lesions and between the organisms, however, justifies their comparative study. In this investigation the method of superinfection has been intensively employed.

Geographical Distribution of Leprosy in the Rodent Species.

Since the original discovery in *Rattus norvegicus*, the majority of rat leprosy infections have been noted in that species. However, other rodents have been found infected. An infection of *Rattus rattus* was recorded from India in 1907. Kawamura, prior to 1910, recorded an infection of *Rattus rattus alexandrinus* from Japan, while Asami (1932) followed with an infection of *Rattus rattus*. Lampe and De Moor (1935) recorded infections in various species, including *Pachyura murina* and *Mus musculus humourus* from Batavia. Details of these are included in a paper by Lowe (1937), who recorded the finding by Boyé (1931) of an infected opossum. Derrick (1936), from Brisbane, Queensland, records two *Rattus rattus alexandrinus* infections. Krakower and Gonzalez (1937), in Puerto Rico, found an infected *Mus musculus* and claimed priority over Lampe and De Moor. Lowe (1939) records a natural infection in *Bandicoota indica* from India; while Badger (1936) has added Hawaii to the list of places. The first Australian record of a leprous rat was made by Tidswell (1904); since then leprous rats have been recorded from various parts of the continent. The New South Wales Department of Public Health records now reach 16 infected animals, 14 *Rattus norvegicus* and two *Mus musculus*. The mice are here recorded together with two additional examples of *Rattus norvegicus*. I have also to add a further infection of *Rattus norvegicus*. The records of examinations of rats from leprosaria are scanty. Soule (1934), at Culion in the Philippine Islands, recorded negative results, and Itihara (1939) from Shorakuta in Korea, recorded positive results in 6·6% of the rats examined. This distribution in rodent species I think is significant, and in future special attention should be given to native rodents on the islands away from civilization. A close examination of domestic animals such as the cat and dog, particularly in leprosy infected areas, appears necessary.

Distribution of Organisms in the Body.

The distribution of organisms in the body of the rat is found to be more generalized the more thorough the search. The list of affected organs given by Lowe has been greatly supplemented by Krakower and Gonzalez (1937 and 1940) and by my own records in this paper. The female sex organs are stated to be more highly infected than those of the male, but my experience has been confined to male animals. Little attention has been centred on infection of the skeletal system. A number of heavy infections of the sternum, particularly at the xiphoid process, is here recorded. The blood vessels show little evidence of infection, but a few scattered organisms may be noted. Infection of the glandular system is variable, but may be noted early after skin invasions. Experimentally all superficial glands may be infected simultaneously, or any one area may be implicated. This depends on whether the inunction was carried out over the whole or portions of the ventral surface of the animal. Besides the inguinal, axillary and cervical glands, the preputial glands are sometimes the site of a heavy infection. Whatever the exact

function of the latter glands, frequent examination of them suggests that they act as a collecting base for all types of organisms. In the nervous system generally no pathological changes are found, but an occasional organism may be found in the cord and brain. Marchoux and Sorel (1912) found the urinary system highly infected. Lowe found organisms, but no lesions. Dean (1905) found bacilli in the kidney capsules, and McCoy (1908) found bacilli in the bladder. In the kidney capsules I have found both pathological changes and organisms, similarly in the bladder and the bulbo-urethral (Cowper's) glands, and also, as noted above, in the preputial glands. The record of Krakower and Gonzalez of lepra cells in the pancreas has been confirmed by me. Lowe considers that, apart from infection of the liver and salivary glands, the digestive system is unaffected. This is incorrect, since I have found a graded infection of the stomach, pylorus and duodenum, with lesions in the stomach. In my experience such infections are very much heavier in experimentally infected rats than in those naturally infected. The organisms in the fæces are in such large numbers that they can no longer be considered merely as elimination products.

This discovery, associated with De Souza-Araujo's fæcal globi, suggested a new method of attacking the transmission problem of rat leprosy. The investigation has been repeated in a series of animals. The first evidence of such an infection was noted in one of my experimental series. Since then all rats kept for a long period were in a similar heavy state of infection. Natural infections, too, varied from light to fairly heavy stomach invasions and have occurred in *Mus musculus* and *Rattus norvegicus* (included in the latter are the latest New South Wales additions). Such heavy fæcal contamination obviously indicated a pathological leakage somewhere in the alimentary tract. It was therefore considered necessary to examine serially and systematically the whole length of this tract in each specimen. The whole tract from tongue to anus was opened, washed and fixed in a 10% solution of formalin, the long portions being rolled and fastened to ensure control of anterior and posterior positions. After dehydration, clearing and embedding, sections were cut, stained and examined. The examination revealed a heavy infection in the stomach (Figure XVII) with destruction of the mucosa at the cardiac end, and a progressively decreasing infection through the pylorus to the duodenum. The rest of the tract was either unaffected or contained only loose organisms scattered in one or two places. After either inoculation or inunction of the skin of laboratory animals, a few scattered organisms may be found in some distant parts of the body; but no real concentration or colonizing was observed at other than the experimental sites. Natural infections, on the other hand, usually produce fairly widespread invasions of the skin of the body, associated with superficial lesions around the nose, ears, tail and feet. Invasion is prominent sometimes with ulcerations and almost complete destruction of the ears. Lowe (1934), however, makes the following statement:

> There is no general invasion of the skin until the animal is moribund with a massive general infection, and even then the multiple skin lesions are merely post-mortem findings detectable by smears or sections but not clinically.

While the latter part of Lowe's statement may be correct, he was dealing with inoculated rats; the first part is certainly incorrect, as repeated inunction with emulsions of organisms results in extensive bacillary invasion of the skin associated with clinical lesions and intracellular organisms long before extensive internal lesions can occur. Fæcal organisms having been found capable of infecting rats by passing through the skin, sections of those portions of the surface of the body—including appendages—contacting the ground were examined, in order to see whether there was an association of internal and external infections. Examination of the sections showed in most cases definite invasion of organisms in the skin proper and the dead epithelium; organisms were also found in the associated external debris. Frequently such debris around the tail and ears contained many bacilli. The feet—probably because they are cleaned more regularly by the animal—are, however, free from debris. In the two mice only one ear was complete; the others had been eaten away by ulceration. The remaining portions of the ear were heavily charged with bacilli, as also was the associated debris. The distribution of the organisms is therefore much more generalized than has been hitherto realized, and to the list put forward by various authorities the following locations should be added: stomach, pylorus, duodenum, pericardium, bulbo-urethral and preputial glands and sternum. The latter site, which was usually heavily infected, suggests the necessity for a complete search of the skeletal system for organisms, while the finding of bacilli in associated debris provides a link between soil contamination and dissemination of the disease as suggested by Walker and Sweeney as well as by Lampe *et alii*.

Estimation of the Daily Urinary and Fæcal Elimination of Bacilli.

As ordinary smears gave no real idea of the number of organisms voided, the Breed (1911) milk bacterial count was adopted. The numbers in the urine were comparatively low, varying between 1,500,000 and 3,000,000 organisms per cubic centimetre. Since rats may void about six to seven cubic centimetres of urine per day, the daily elimination would be up to a maximum of 21,000,000 organisms. Fæcal eliminations were on a much higher level. After the fæces had been dried, the daily average fæcal output was found to be 2·05 grammes per rat. For estimations 0·45 gramme was emulsified with water to make 15 cubic centimetres of emulsion (a mortar and pestle being used). The resultant emulsion was sieved through muslin and excess of water was squeezed out. The Breed count gave the result of 50 organisms per field, which equalled 15,000,000 per cubic centimetre; this in turn meant that there were some 225,000,000 organisms in 0·45 gramme of the dried fæces. Since 4·5 times this amount of fæces is passed daily by each rat, approximately 1,012,500,000 organisms are excreted every day. However, many organisms remained in the residue after the material had been filtered, and some allowance for this should be made; 1,250,000,000 bacilli may be taken to be a fair estimate. In these fæcal emulsions, while the majority of organisms are loose, many bundles and globi (Figure XVIII) may be observed in smears.

Morphological Characteristics and Staining Properties of Organisms.

Attention has frequently been drawn to the similarity in morphological and staining characteristics of human and rat leprosy organisms. Francis has recently directed attention to similar features in Johne's disease bacillus. Pleomorphism of the leprous types has been stressed, and Walker (1929) included a variety of organisms as stages in the development of the human leprosy bacillus. Most of these varieties have, however, been associated with culture work and are almost certainly contaminants, which would in no circumstances be accepted if found associated with animals. The granular-coccal type of organism suggested by Hoffmann (1935) is, I agree, a definite stage in the life cycle; but his claim that the organisms may vary down to the limits of visibility is inadmissable and throws doubt on his granular type. My observations on direct infection, or superinfection through the skin of the animal, indicate merely variations in the length of the bacilli, from the coccal-Hoffmann granule to the long rod form, with little difference in the thickness of the organisms. Rogers and Muir (1940) give measurements of 1·0μ to 8·0μ for the human type; these are generally uniformly stained except after the lepra reaction, when they are granular or beaded. The measurements of the rat organisms are, according to Stefansky, between 3·0μ and 5·0μ. An affinity between the two has been claimed by Rabinowitsch (1903), who considers that they can be differentiated from the cultivable acid-fast bacilli. Marchoux and Sorel differentiate the rat organisms from those of the human by the absence of parallel arrangement, gloea and globi. De Souza-Araujo (1938) disputes this, holding that these features are prominent in the rat organism, and with this I am in agreement. Measurements of human and rat organisms that I have carried out

reveal no material difference in size, both types varying in length from the Hoffmann granule of less than 1·0μ to the long rod form up to 12μ in length. The Hoffmann granule is distinct from the granular or beaded organism; it is viable and considered to be the early stage of the rod. Division of the rod form may be, firstly, into shorter rods, with subsequent division to the granular type or directly to the Hoffmann granules. Comparatively little is known about the organisms usually termed granular or beaded types; they are perhaps degenerate organisms or again a product of faulty technique.

Cowdry and Heimburger found that beaded bacilli were a feature after fixation, but not in frozen sections. Manalang considers them a product of treatment. Recently Yegian and Baesden (1942) have found that beading in tubercle bacilli is caused by faulty preparation or concentration of the stain, and can be rectified by merely soaking stained smears in neutral alcohol. In human and rat leprosy lesions, however, the organisms may be of both block and beaded types, the latter appearing mainly in long-standing ulcers. I have not noted these in primary ulcers or in urine or fæces. Staining variants appear to be mainly cultural in origin. It has been held that some organisms are acid-fast on one medium and acid-sensitive on transfer to another; but whether the medium itself is responsible is uncertain. After ingestion of organisms by lice, Thierfelder (1936) found complete early loss of acid-fastness. Van Breuseghem (1937) found no loss in acid-fastness after twenty-two days in the leech and after double that time in storage water; between such extremes vitality and acid-fastness have been found unimpaired. Asami (1932) records acid-fastness intact for four and six days in fleas and cockroaches. I have similar records for fleas and a shorter period for rat lice, with apparently no interference with viability, structure or acid-fastness. Book-lice, which for some weeks gained access to my store of dried infected fæces, yielded well stained organisms, as did the fæcal pellets from the book-lice and the original fæcal specimens. Nor were changes, structural or staining, seen in the organisms of nematodes (*Protospirura* species) recovered from the stomach of an infected *Rattus norvegicus*. Examination of sections of these revealed numerous bacilli.

Origin of Lepra Cells.

Confusion exists as to the origin and type of lepra cells. A common origin has been suggested in human and rat leprosy. Oliver (1926) states that the diameter varies from that of a lymphocyte to several times this length, the cell having a large amount of protoplasm associated with vacuoles and a single nucleus, which is forced to one side by numerous organisms. A search of the literature indicates that a variety of cells has been implicated. Cowdry (1938) suggests a common designation for these cells. He found that peripheral "lepra" cells were much larger than those centrally situated, the latter being usually associated with polymorphonuclear leucocytes. Lewis (1925) makes the following statement:

> Just what term should be used to designate these cells does not decrease the importance of the fact that macrophages, epithelioid cells and giant cells do arise from the leucocytes of the blood, without, in this case, any possibility of participation in the phenomenon by the endothelium or the connective tissue.

According to Cowdry, Lurie refers to the "impotent" polymorphonuclear cells, and Black considers that the neutrophile cells play no part in leprous lesions. Denny and Eddy (1933) associated polymorphonuclear cells with globi formation. These were produced in tyrode fluid inoculated with rat organisms or with human pus, but not with human leproma organisms. Gay (1924) suggests that macrophages dispose of animal cells, including polymorphonuclear cells with ingested bacteria; he states that "they are responsible for phagocytosis of certain more chronic bacterial infectious agents such as the tubercle bacillus and the bacillus of leprosy". He also considers that the two main factors in the disposal of bacteria under conditions of natural and acquired immunity are polymorphonuclear cells and antibodies which are operative both locally and generally in the animal body. Metchnikoff (1905) stressed the importance of the polymorphonuclear cells or macrophages in bacterial infections. They collect locally in areas of inflammation, increase in the general circulation and can be seen to engulf and digest the bacteria. Gay suggests that "the evidence for the importance of the polymorphonuclear cells in protection is overwhelming, it has become increasingly evident however that these particular cells do not account for the entire sequence of events in protection against bacteria, and the accumulation of microphages in large numbers is usually a happy prognostic significance, their absence unfavorable". Owing to the evident association of intracellular organisms and superficial lesions of leprosy, it would appear that the latter portions of this statement should be reversed, while claims concerning the protective value of invaded cells and the digestion of intracellular organisms are questionable. Krakower *et alii* (1943) consider that there is no clear evidence that bacilli, alive or dead, can be digested by the cells of the host. Oliver points to the tissue culture work of both Lewis and Maximow (1924), who suggest an association with the blood cells. Claims have been made that leprosy organisms are all intracellular and that loose organisms are from ruptured cells; these claims are doubtful. I have noted organisms in sections at different levels, and their presence in such positions is obviously no mere accident. Confusion on the types of invaded cell in leprosy has arisen because lesions studied were of unknown duration. This made it impossible to observe the sequence of invasion of cells during development. Such sequence can be seen in Figures VII to IX, since invasion of cells occurred between the tenth and twelfth days in the polymorphonuclear leucocytes. No explanation has yet been given for the appearance of the cigar-bundle, nor for the non-nucleated cells. The last-mentioned have been classified sometimes as lymphatic vessels containing a jelly-like substance and bacilli, but are more probably polymorphonuclear cells whose nuclear structure has been destroyed by the organisms. Superficial lesions are certainly associated with superinvasion of bacilli, the type of lesion being due to variations in attained virulence. Primary inunction with an emulsion is frequently followed by a temporary inflammatory thickening. Examination reveals scattered bacilli for varying periods. Subsequent treatment with emulsions is followed by progressively stronger invasions of organisms. These gradually disappear from the skin. When resistance has been broken down, the organisms become more persistent and intracellular. About this time superficial lesions can be seen, papular, nodular or granulomatous according to the virulence of the invading organisms. These lesions are now permanent, the papular and the nodular sometimes gradually merging to form the granulomatous type of lesion which subsequently ulcerates.

Cook (1927), in a discussion on the effect of sunlight, makes the following observation:

> Leprosy results when these phagocytes are incapable of destroying the invading organism, which multiplies in their cytoplasm after ingestion.

Sometimes loose organisms may be found in the skin at a distance from the site of infection. It would appear obvious that these had been transported without the aid of the leucocytes, probably through the blood or lymph channels. Mazza (1924-1925), according to McKinley, suggests an immediate mobilization of polymorphonuclear cells, which are invaded by organisms and then transported to the rest of the body. Superficial lesions produced by superinfection are not associated with an immediate mobilization of leucocytes. Multiplication of organisms first takes place, bringing about the inflammatory condition so necessary for the mobilization of cells. The cells, mainly polymorphonuclear leucocytes with a small number of lymphocytes, are invaded by comparatively few organisms (Figure X); but sometimes examination of the polymorphonuclear cells reveals prodigious invasions of bacilli (Figures XI and XII), gradually filling the protoplasmic space and forcing the nucleus eccentrically. At other times there is evidence of destruction or splitting of the nucleus into large or small portions variable in

number (Figures XII and XV). At other times the cells appear to have lost all their nuclear element (Figure XVIII). Krakower *et alii* (1943) makes the following statement:

> The bacilli thus released from necrotic cells are again taken up by histiocytes whether primarily through the disintegration of the polymorphonuclears which appear with the necroses and have phagocytized bacilli, or directly due either to the inwandering of new histiocytes or of adjacent lepra cells.

Such nuclear changes are, in part, explained by the tadpole work of Clark and Clark (1920 and 1923), who produced inflammatory conditions at the sites of croton oil injections. The polymorphonuclear leucocytes migrated toward these sites, where they became stationary, and had spherical nuclei, sent out processes and came to resemble fibroblasts; as the inflammatory condition subsided the cells again became amœboid and wandered away. However, since leprous lesions are in a more or less constant inflam-

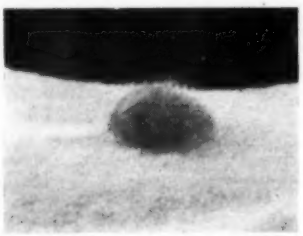


FIGURE II.—Rabbit nodule eighteenth day after injection with organisms. (Natural size.)

matory state, no real return to a state of normality of the mobilized leucocytes could be expected, but rather deterioration inside the cells, though perhaps not of the enclosing membrane. The difficult task of following up the sequence of events in polymorphonuclear cells after their invasion with organisms would certainly require a great many smears made at regular intervals, and such collections are gradually being built up from various cases.

In superficial lesions, however, no change from one type of cell to another has been found.

As to specificity, the production of a granulomatous lesion containing intracellular organisms early after inunction with an emulsion containing acid-fast organisms,

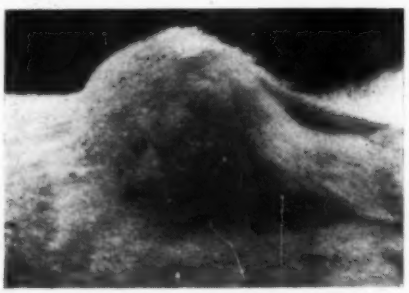


FIGURE III.—Nodule 56th day after injection with organisms. (Two-thirds natural size.)

appears to be adequate proof, particularly since in one case these organisms had been passed from a rat granuloma by inoculation successively through a guinea-pig → rabbit → rat → rat → inunction on rat sequence to produce a granuloma with intracellularity of acid-fast organisms and typical ulceration.

Viability and Virulence of Organisms.

Saprophytic mycobacteria are known to be free-living organisms; comparatively little is known of the survival of the pathogenic group outside the body. *Mycobacterium tuberculosis* has been shown to be still viable after passing through a septic tank system (Cummins, Davies and Acland, 1929, and Morgan, 1929), although obviously the period of exposure is uncertain. With regard to the organisms of human and rat leprosy, much has been said about degenerate organisms, but no exact criteria have been put forward showing exactly which are degenerate. Information on viability and virulence is likewise scanty. Lowe stored leprosy bacilli in a moist condition outside the body and found them to be still pathogenic. Marchoux (1934) kept them in glycerine in the refrigerator for four years and found them to be still viable, but considered that vitality had been destroyed after twelve days at 37° C. or after fifteen minutes at 60° C. It is usually considered that such organisms are killed by exposure for long periods to weak acid or antiformin. However, I have noted that contact with antiformin for twenty-four to forty-eight hours has comparatively little effect on the fæcal bacilli of rats; I found such organisms to be of equal virulence to fresh organisms, being equally capable of invading the skin of rats and producing clinical lesions (Figure VI) by superinvasion. These lesions are further associated with mobilization of the polymorphonuclear leucocytes which are invaded by the organisms. Experimental evidence, however, indicates that the virulence of the bacilli of fresh fæces is greater than that of the same fæces stored dry at room temperature for twelve to fifteen or more months. Although both are

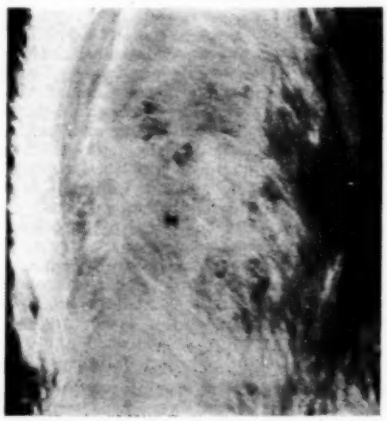


FIGURE VI.—Superficial lesions of abdomen of rat fourteen weeks after inunction with fresh fæcal organisms. (Natural size.)

capable of producing lesions, the latter take much longer. The fresh fæcal organisms appear to be much more constant in virulence than the organisms of the urine or those of primary ulcers, for while the organisms in urine or from ulcers are at first very virulent, particularly the former even after storage for some weeks, storage for some months appears to lower virulence. Sakurai (1936) obtained invasions of intact skin and nasal membrane by granuloma organisms, but there were no associated lesions or intracellularity of the organisms. I have had a similar experience with such organisms and with those from long-standing ulcers, even after repeated invasions. However, one may find that the bacilli under these conditions produce a light internal concentration in the various organs, but there was a tendency in some cases to immunization of the animals, and this is invariably followed by disappearance of the organisms from the inguinal and axillary glands. From these results it has been deduced that the bacilli of granulomata and long-standing ulcers have a low standard of virulence, while the virulence of organisms from primary ulcers, urine and fæces is on a higher plane. Apparently some unknown factor influences increased virulence. An increased inflammatory condition in the ulcer may be suggested; but is the same condition a constant feature of the stomach and the bladder? The constancy of the fæcal organisms in producing lesions partly answers the enigma of Fite's results with a mixture of bacilli and gastric mucin, but the whole picture is not yet complete.

For the production of superficial lesions two things appear to be necessary. The first is the breaking down of local or general resistance accomplished by repeated inunction or by subcutaneous inoculations with any of the various types of organisms. The second is the use of organisms of a naturally high order of virulence, such as those from the fæces or urine, or the use of organisms of long-standing ulcers or granulomata whose virulence has been built up by passage through other animals, as the guinea-pig and rabbit, by subcutaneous inoculation. Internal infection of rats may be obtained by the agency of fairly large numbers of rat lice: (i) by feeding them

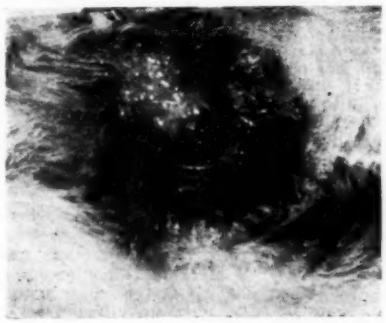


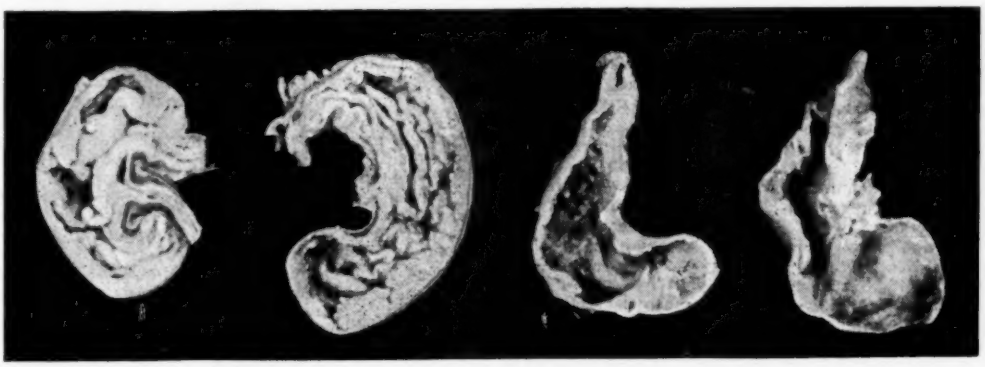
FIGURE XIII.—Ulceration of abdomen 230th day after inunction or twelve days after breakdown of lesion. (Approximately natural size.)

on the animal, (ii) by inoculating an emulsion subcutaneously or (iii) by inunction on a single occasion. Infection producing internal and external clinical lesions having also been obtained by continued inunction with fæcal and urinary organisms, no further reason exists for doubting that natural infection in wild animals is the result of repeated contact with soil infected by organisms voided in the rat ejecta or in the ejecta of ectoparasites passed directly on to the skin during feeding operations.

The first evidence of infection by superficial lesions in my series was obtained by breaking down resistance by combining inoculations of small doses with inunction with large numbers of organisms. Virulent organisms for the final inunction were produced by passage through a guinea-pig, which showed a pyramidal-shaped lesion with organisms (Figure I) reaching a maximum diameter of 17 millimetres in seven days. Subinoculated into a rabbit, bacilli from this lesion resulted in a non-vascular nodule of maximum measurements of 44 millimetres in about thirty days (Figures II, III and IV). Subsequently the lesion broke down after an inflammatory reaction, and the organisms being injected into a rat produced a nine-millimetre nodule, the washings of which were injected into the same rat on the fourth day and resulted in a lesion measuring twelve millimetres by seven millimetres. Both these rat lesions ulcerated three days later. Breed counts of bacilli from washings of these ulcers resulted respectively in one to ten fields and two organisms per

FIGURE XVI.—Rat showing generalized internal infection. (Half natural size.)

field. Inunction on three rats with the second washing diluted to contain 60,000 organisms resulted in a permanent lesion in one rat. In all rats inflammatory reactions occurred with thickening of the skin; these reactions subsided in two, but the other was granulomatous, covered the whole treated area by the sixth day and contained loose bacilli; these were obviously increasing in number. By the eighth day a Breed count of skin serum yielded sixty bacilli per field, which was equal to 18,000,000 per cubic centimetre; on the twelfth day many organisms had invaded polymorphonuclear leucocytes, which had now been thoroughly mobilized. Owing to interference six



A B C D

FIGURE XVII.—Stomachs of rats, showing graded destruction of the cardiac end. A: normal rat. B: light destruction in rat. C: medium destruction in white rat. D: heavy destruction in white rat. (About one-quarter above natural size.)

weeks later the lesion broke down, but gradually healed, breaking down permanently some eleven weeks later (Figures XIII, XIV and XV). The animal died nine months after primary inoculation from an extremely heavy generalized infection (Figures XVI and XVIIb) which was reflected in the uro-genital and alimentary systems. The two rats in which skin thickening subsided were killed at 17 weeks and at 22 weeks respectively; in neither were internal abnormalities detected. The last-mentioned rat showed no evidence of infection in lesions or organisms; in the former, however, bacilli were found in kidney capsules, spleen, heart, liver and inguinal glands.

Resistance and Immunity.

The susceptibility of rats to rat leprosy is well known, but the percentage of rats showing generalized infections is very low. This no doubt is due to the fact that wild rats are sometimes trapped fairly early in the disease, and that in experimental series either the animals are sacrificed early or they have been inoculated with organisms of unequal virulence. Experimentally Lowe claimed to have achieved infection in 100%, but did not give clear evidence of generalized infections. In San Francisco Walker and Sweeney (1929) found the rate of natural infections in rats to range from 28% to 79%. Both these findings are in general higher figures than in other parts of the world. The terms "susceptibility" and "immunity" seem to be used loosely without any clear understanding of local conditions. It has been suggested that susceptibility is brought about by possession of monocytes favourable to multiplication. This appears to be questionable (Figures VII to IX). In laboratory animals variable infectivity is usually decided either by variable resistance or by natural immunity. The question of virulence of the organisms is rarely considered, and Krakower *et alii* suggest that little is known about variations in virulence. Comparatively little attention has been paid to, and no real success has been attained with, immunization, probably because of the absence of suitable emulsions. Wherry (1909) claimed to have retarded infection after injections of killed bacilli. Lowe, under similar conditions, obtained no clear evidence of immunity. Muir and Henderson (1928) had similar results with an emulsion of Calmette-Guérin bacillus. Markianos (1929) had retardation effects with defatted organisms. Marchoux (1934) found the inguinal glands infected in a wild rat, but when the animal was killed some weeks later examination gave completely negative results; he considered that good nutrition and hygiene had been responsible for the disappearance of the organisms. The experiments here recorded show that the factors responsible for the change were lack of opportunity for reinfection, together with an immunity produced by organisms of low virulence. In 1944 I drew attention to variable receptivity and retention of organisms both deep and in the skin of various animals; probably these are the result of variations in resistance. After primary invasion of the skin, organisms may remain in rats for one to forty-one days, in guinea-pigs for six to twenty-one days, and in rabbits up to four days only. It should be pointed out that, although prominent reactions occurred after subcutaneous inoculations in rabbits and guinea-pigs, the animals did not show infection in the true sense, even when inoculations were repeated again and again, and even after repeated intravenous inoculations. Marchoux's experience has been repeated in my series of rats. The occurrence of infection was demonstrated by the loose and intracellular bacilli in the skin, together with invasion of glands as shown by hypodermic washings and sometimes a few small papular lesions. When the animals were killed about two months later, all evidence of infection had completely disappeared. It is considered that this condition had been produced by the combination of long periods between inunctions and the use of organisms of lowered virulence; the result was probably immunity in the animals. This question will be settled only when genuine cultures have been obtained and a comparison can be made of serum of such animals with serum of animals showing generalized infections.

Transmission and Inoculation Methods.

Attempts at transmission of human and rat leprosy have been made. Some 145 inoculations with human bacilli gave only two questionably successful results. Animal experimentation has resulted in more success, but only in later years. De Souza-Araujo (1931) and other workers have obtained positive evidence of infection in various animals, while Adler (1938) infected Syrian hamsters. Sir Leonard Rogers, in a discussion on De Souza-Araujo's paper, suggests the use of small measured doses of bacilli, so that multiplication may be estimated:

> In ordinary infection of man presumably only a very few lepra bacilli enter the system through some minute abrasion, such as an insect bite infected by bacilli, or as a result of sneezing over the skin by a leper living in the house. Until infections of animals were produced by similar small numbers of bacilli doubts would remain. Whether any animals were sufficiently susceptible as to be infected by such small doses was doubtful; only experiment could decide.

Bayon, continuing the discussion, goes to an extreme in suggesting inoculation of one hundred mice, a similar number to be inoculated after each infection; the idea behind this suggestion is to separate the living from the dead organisms. He considers that the latter cannot be transferred more than twice. For some time I have been of the opinion that uncontrolled dosing was almost valueless, since no constant control of lesions can be kept; however, I have recently come to the conclusion that the greater the number of organisms used for subcutaneous inoculation, the more severe the initial reaction which appears effectively to increase the virulence of the organisms. This initial evidence of infection did not until recently appear to have been appreciated; the emulsions produce early transient lesions, which unfortunately have been taken as indicating a definite infection without complete follow-up. De Souza-Araujo, McKinley and Soule (1932) and Watanabe (1937) have focused attention on such early lesions; my experiments show this initial evidence of infection to be true, but the lesions appear very much earlier. Transmission by the agency of arthropods has been accomplished by Ichihara (1936) and myself, using infected *Lælaps* and *Polyplax* respectively, and feeding them on healthy animals. Infection has also been attained by inoculation or inunction of emulsions of these insects. Wayson and Masunaga (1935), and also Sakurai (1936), obtained infection through the nasal mucosa. The last-mentioned found that there were no pathological changes; he later considered that skin penetration was more important than that of the nasal mucous membrane. Lowe has asserted that penetration of the skin by organisms is not possible, while De Langen takes the opposite view. Sakurai found actual invasion of the intact skin of mice and rabbits after plucking the hair. My experience confirms the results of this author; on scarified areas the organisms appear to be more invasive. Marchoux and Sorel failed to infect young rats through intact skin; but Marchoux and Chorine (1939) succeeded with older rats after depilation. Lampe *et alii* (1936) stated that after shaving the animals, and using mud from an infected rat-run, they produced infection in rats; later (1938), however, they withdrew their claim. Cowdry considers infection by soil as improbable and the evidence weak, but goes on to state that "mycobacteria coming from individuals or animals or conceivably from soil, gain entry through the skin or nasal mucous membrane and produce lesions". While invasion of the skin undoubtedly occurs, it does not necessarily constitute infection in the true sense; it may become so by super-invasions. In controlled, heavily infected laboratory rats, although a few scattered—loose or extracellular—organisms may be recorded in various parts of the skin, there is no concentration or intracellularity of the organisms at other than the experimental sites. Naturally infected rats having a musculo-cutaneous infection with organisms (intracellular) in almost all parts of the skin, do not always show evidence of generalized infection by internal lesions. The number of bacilli that have passed through the intact skin has been estimated by using inunctions on measured areas of the skin for one or two

hours before cutting the area out and setting it on cork for fixation, or by fixing the entire animal in a 10% solution of formalin. In one experiment some 6,000,000 organisms were soaked for two hours on the area; the animal was fixed whole, after which the skin area was cut out and again cut into small measured pieces for dehydration, clearing, embedding; sections were made and some of these were cut, stained and examined. The examination showed that the organisms were definitely invasive and fairly evenly distributed. The calculations for the whole of the treated area worked out at 40,000 actual invaders; this, it will be noted, was 1/150 part of the number of organisms originally used. However, the question arises whether all the organisms which gained entrance to the skin were localized or whether they had migrated to other parts of the body. Similar experiments were carried out; the results, although showing variations, closely approximated the figure given above. Sakurai has shown that a single treatment with granuloma organisms, while producing invasion of the skin, produces no pathological changes or clinical lesions; this is equally true after repeat invasions with the same type of organism. However, when treatment is continued with another strain of organism—early ulcer, urine or fæces—evidence of pathological changes or superficial lesions is in most cases soon forthcoming; this is subsequently followed by deep or generalized internal infection. The appearance of the superficial lesions, which occur at about the same time after the final inunction, shows some variation in type, from a papular or nodular type to a granuloma associated fairly closely with intracellularity of organisms. This variation in the type of lesion appears bound up closely with a variation in the virulence of the organisms used, the less virulent forms giving rise to the papular or nodular lesions and the more virulent to granulomata. Such lesions are permanent, while inoculation lesions are temporary only.

Clinical Lesions: Are They Primary or Metastatic?

A considerable amount of controversy has arisen on the question whether clinical lesions are primary or metastatic, the consensus of opinion being in favour of metastasis. Plantilla (1936) considers that superficial lesions are primary in origin and result from contact with such things as the floor, chair, bedding or even soil. McKinley and Soule (1935), and Watanabe (1935), by inoculation with culture or granuloma emulsions, produced lesions in from seven to twenty-one days. Subsequently at various times these either ulcerated or were absorbed. It was considered by Watanabe and De Souza-Araujo that sensitization was the result of primary inoculation, subsequent injections producing larger lesions and decreasing the incubation period; obviously they mean local lesions and not a generalized infection. In this inoculation series, rats, guinea-pigs, rabbits and kittens were used, and various emulsions such as granulomata, ulcers, pus from nodules, urine, arthropods and hæmolyzed blood were employed. Injection of these produced papular or nodular lesions, which were frequently prominent in two to three days and of maximum size in three to six days. Rats showed hard nodules, in diameter five to seven or occasionally even twelve millimetres, guinea-pigs and kittens showed soft pyramidal nodules up to seventeen millimetres in diameter, and rabbits showed hard, non-vascular nodules up to a maximum of 44 millimetres in diameter. Arthropod emulsions injected into rats produced lesions of a diameter up to six millimetres, and hæmolyzed blood produced lesions two to three millimetres in diameter. The lesions so produced were absorbed or ulcerated after various intervals. I have failed to record whether organisms were present in the skin over those lesions which were absorbed; but invariably they were recovered from the ulcer proper and frequently in the peripheral skin of such ulcers. However, I have been unable to decide which type of lesion is the more important in the production of generalized infections. Of over 100 tests (primary and repeat), a small proportion failed to produce reactions; in two-thirds ulceration occurred in from three to fifty-three days. Superficial lesions produced by skin inunctions require a number of such treatments; the results can, however, be considered purely as primary lesions which make their appearance some days after the final inunction. The type of lesion produced, as stated, varies with the virulence of the organisms used for final inunction, and this raises the question whether the papular subcutaneous lesions illustrated by Krakower and Gonzalez are really the result of metastasis or arise from external invasions of virulent organisms. I have obtained lesions similar in appearance and of a permanent character after slit-probe subcutaneous inoculations. However, this does not completely rule out the possibility of the production of superficial lesions by metastasis when the disease has a good hold of the animal; but in the present state of our knowledge it is impossible to be definite on this point.

EXPERIMENT XVII.—A rat was subjected to repeated subcutaneous inoculations. On the first day it was inoculated in four places with 0·1 cubic centimetre of rabbit pus washing; no reaction occurred. On the fourth day it was inoculated with 0·8 cubic centimetre of rat ulcer washing; no immediate reaction occurred, but on the third day after the inoculation a lesion eight millimetres in diameter was present, and on the ninth day after the inoculation the lesion ulcerated. On the ninth day the animal was inoculated with 0·5 cubic centimetre of guinea-pig pus washing; there was no immediate reaction, but on the third day after inoculation a lesion ten millimetres in diameter was present, and on the fourteenth day after inoculation the lesion had absorbed. On the twelfth day inoculation with 0·15 cubic centimetre of kitten pus washing was carried out; a small papule appeared on the second day after inoculation, and was absorbed on the fourth day. On the thirty-fourth day inoculation with 1·0 cubic centimetre of rabbit pus washing was carried out; there was a reaction on the fourth day after inoculation, the area being 9·0 millimetres in diameter, and on the seventh day ulceration occurred. On the thirty-eighth day the animal was inoculated with 0·5 cubic centimetre of washing from the immediately preceding lesion; on the second day after inoculation there was a reaction affecting an area measuring 12·0 millimetres by 7·0 millimetres, and ulceration was present on the third day. On the forty-first day a smear from the ulcer caused by inoculation of rabbit pus washing (on the thirty-fourth day) was examined, one bacillus to ten fields being found, and in a smear from the ulcer produced by inoculation of washing from this ulcer (thirty-eighth day) two bacilli per field were seen. The ulcers were open for eleven days and then gradually healed, leaving no trace of the lesions apart from slight alopecia at the site. On the sixtieth day 0·3 cubic centimetre of rat ulcer washing was inoculated; on the third day after inoculation the area of reaction was 9·0 millimetres in diameter, and on the sixth day it had absorbed. The rat was killed on the sixty-ninth day; post-mortem examination revealed no internal abnormalities, but loose organisms were found in the skin at the inoculation areas, in the kidneys and in the spleen.

Natural Infections: Are They Simple or Superinvasions?

The question whether natural infections result from simple infection or superinfection has been debated for many years, and Wherry (1908) stated that Joly pointed out that Sabrazes held the view that leprosy might be produced by a large number of small inoculations, such as parasitic insects might inflict. Vespoli (1936) considered that superinfection was a necessity, and Marchoux that secondary infections favoured generalization of the bacilli in rat leprosy. Schobl *et alii* (1930) thought that repeated inoculations resulted in reactions of decreasing intensity associated with increased resistance—a view opposed to that held by McKinley and Soule, by De Souza-Araujo and also by Watanabe. De Langen (1931) pointed out that superinfection through the skin was possible. It is, of course, recognized that one inoculation will produce infection of rats, but does not result in a generalization of the disease—namely, in widespread internal and musculocutaneous lesions. Primary subcutaneous lesions localized to the injection site are temporary structures which may be absorbed or may ulcerate; this is also the site of the later permanent lesion containing loose and intracellular organisms and subsequently a permanent ulcer. It is of interest to note that in the primary lesion after ulceration the peripheral edge frequently contains organisms, while after absorption the skin appears to be devoid of

organisms. My experience of repeat inoculations left me with the impression that, although the size of the reactions varies, this was not due to sensitization, but rather to variation in the virulence of the organisms used. No reliance could be placed on the time of appearance, of subsidence or of ulceration, even when the inoculation was made with controlled emulsions of organisms. Hypodermic subcutaneous injections result in single lesions, but after the slit-probe subcutaneous inoculations the lesions are multiple, becoming prominent in a couple of days or so, and may be papular or nodular, sometimes attaining a diameter of more than seven millimetres. Such lesions may be absorbed or may even ulcerate through the skin. Secondary introductions appear to result in more permanent lesions, which are subcutaneous, but they do not appear to coalesce to form granulomata, at least on the basis of the times allowed in my experiments. Examination of smears or sections of these small lesions reveals innumerable organisms. The balance of the experimental series was designed to approach as near as possible to natural conditions. Inoculation was by inunction, either on intact breast or on scarified abdominal skin, or on both. The primary, secondary and some subsequent inunctions were usually associated with invasions of the skin by organisms in both areas; these in the early stages were loose and eventually disappeared. Later invasions with more virulent organisms were invariably followed by closely associated intracellularity of organisms, or by lesions, or by both; in one animal, three treatments only were necessary for the production of papular lesions, subsequently followed by a granuloma, ulceration and internal lesions of a light generalized infection. In most of the experiments, however, multiple invasions were necessary before clinical lesions became obvious; but these were by no means consistent in their appearance. The arthropod experiments were with fleas, mites and lice, mainly by inoculation of emulsions of these insects. Infection was also produced by inunction on scarified skin with emulsified lice and finally by feeding infected rat lice on the animals. The two last-mentioned methods were by single applications of about 100 to 150 lice or emulsions of these, and although they resulted in the internal appearance of organisms, they were not associated with either internal or external macroscopic lesions. Most of the positive experimental (clinical) results have been obtained with urinary and fæcal organisms, but only after multiple invasions. Since large numbers of organisms were used in these experiments, it is logical to conclude that in nature the time factor would be more prolonged and the number of bacilli at each presentation would be much smaller. However, contact with the infected soil or with infected arthropods would undoubtedly be at more frequent intervals and would thus counterbalance experimental invasions; furthermore, bites and abrasions in wild animals would certainly have their influence. It has been shown that superficial lesions appear only after repeated invasion of the skin by organisms; consequently it would appear that the viewpoint of Sabrazes may be upheld, and that regular "transfers" of infected arthropods would result in the production of superficial lesions as well as in more definite internal infection of the animals.

Arthropods and Rat Leprosy.

Evidence of infection of ectoparasites with the organisms of rat leprosy appears to have been noted first by Wherry (1909), who found infected lice. Marchoux and Sorel (1912) found infected mites, but discarded their results because mites from clean rats were also infected; these latter mites, I suggest, may have recently transferred from an infected animal. Priestley (1913) dismissed a similar finding as of no consequence. Marchoux and Chorine allowed the transfer of infected mites and lice from a killed leprous rat to two other rats in sequence, finding that the arthropods still harboured organisms. It is, however, unfortunate that they sacrificed these animals instead of collecting the ectoparasites and allowing time for the laboratory animals to show signs of infection. I have found typical organisms in the following ectoparasites: *Lælaps* sp., *Xenopsylla cheopis*, *Leptopsyllus segnis*, *Ceratophyllus fasciatus* and *Polyplax spinulosus*. A reexamination of one of Priestley's rats revealed infected *Xenopsylla cheopis* and *Ceratophyllus fasciatus*, while *Ctenocephalides canis* and *Ctenocephalides felis* collected on a leprous rat or fed on a granuloma were proved both by smears and by inoculation to harbour no organisms. Inoculation with emulsions of *Xenopsylla cheopis*, *Ceratophyllus fasciatus*, *Polyplax spinulosus* and a *Lælaps* sp. gave papular or nodular type lesions which subsided or ulcerated. Marchoux infected scarified rats with flies fed less than twenty-four hours previously on a leprous lesion. Markianos (1929) infected rats with pulverized lice injections, but failed by feeding the lice on or to the rats. Ichihara (1936) produced infection in rats by inoculating an emulsion of *Lælaps nezumi*, and by feeding the ectoparasite on rats. Currie and Hollman (1913) kept clean and leprous rats together in the same cage and produced infection. Wayson, according to Lowe, kept clean and infected animals in cages a few inches apart and obtained similar results. It is considered that in both these cases the infecting agent was an arthropod, but the former may have been by urinary or fæcal organisms. In spite of this accumulating evidence of infection by arthropods, Lowe considers transmission by insects uncertain. No attempts appear to have been made to estimate the number of organisms ingested by arthropods; neither apparently has anyone undertaken to find out, by means of examination of sections, the relative distribution of organisms in the arthropod at intervals after an infecting feed. Both these tests I have carried out, using the rat louse (*Polyplax spinulosus*). Emulsions of single lice or batches of lice were made with saline solution (Figure V). Breed smears were made, stained and examined, and it was found that the average number of organisms per louse was 60,000—a very striking result. Marchoux and Chorine have pointed out that infection by arthropods was not by direct transmission, but by fæcal contamination. My observations confirm this. Ejecta passed during feeding operations contain numerous organisms; on the other hand, lice fed on a leproma and stored in dishes pass partially dry fæcal pellets which do not contain organisms. This was rather surprising, since fleas and flies stored in tubes pass organisms freely, but in these cases the fæces are usually of a fluid consistency. The question of direct salivary infection or indirect fæcal contamination of the skin could be settled only by an examination of serial sections of the arthropods. Because of the softer integument, lice were chosen for the work. The examinations of such sections revealed that only the mid and hind portions of the body contained organisms. This finding favours the theory of infection by contamination.

Under the partial famine conditions the organisms would appear to separate out from the fæces as the latter become more compact in the digestive tube. Then, probably, they become entangled in the digestive tube, for in regular feeding operations the digestive tube is flushed out and organisms are found in abundance. Organisms may be retained in infected arthropods after they have fed again on clean animals. These observations have shown that after storage and further feeding, infected lice do not consistently pass organisms in the ejecta. After lice have fed again three and eight hours after an infecting feed, bacilli may be recovered from the ejecta, but, as has been pointed out previously, not in fæcal pellets during storage of the lice; neither were organisms recovered from the ejecta when the lice were left for eighteen hours and fed again. In the animal it was noted after the three and eight hour periods that inflammatory thickening of the skin had resulted from the feeding operations, but there was no such reaction after an eighteen hour period.

EXPERIMENT XII.—A guinea-pig was infected by *Polyplax spinulosus*; 150 of the lice fed on the abdomen. An inflammatory thickening of the skin resulted, and organisms were present in skin puncture smears for ten days. When the animal was killed sixty-two days later the post-mortem examination revealed neither lesions nor organisms.

EXPERIMENT XVIII.—A rat was infected by *Polyplax spinulosus*; 100 lice fed on the abdomen. Again an inflammatory thickening of the skin resulted, but loose organisms were present in skin puncture smear for only five days.

When the animal was killed 124 days later, the post-mortem examination revealed no superficial or internal lesions; but a fair number of organisms were found in the liver, the spleen and the inguinal glands.

EXPERIMENT XVIIIA.—A rat was infected by *Polyplax spinulosus*; 50 lice were emulsified and used as an inunction on the scarified abdomen for a period of one hour. Thickening of the skin, but no inflammatory reaction, resulted; examination of skin puncture smears revealed loose organisms for twelve days. When the animal was killed sixty-three days later, the post-mortem examination revealed no macroscopic lesions, but organisms were found in the liver, spleen and mesenteric glands.

Vitamins and Rat Leprosy.

Statements have been made that vitamin deficiency is a factor in reducing the incubation period and of inducing more virulent lesions in leprosy, both human and rat. Douglas advised De Souza-Araujo to use vitamin-deficient animals in his experimental work. Prudhomme (1937) recorded the cevitamic acid level in rats with rat leprosy lesions. Muir and Henderson (1928) and Kingsbury (1931) considered that vitamin deficiency had no effect in producing more virulent leprous lesions. Lamb (1935) obtained negative results after dietary deficiencies, but held that increased visceral lesions resulted in the presence of a vitamin *B* complex and protein deficiency. Lampe *et alii* (1935) stated that a vitamin B_2 deficiency aided the development of rat lesions, and (1936) that B_1 and B_2 hypovitaminosis was necessary to produce infection. Badger and Sabrell (1935) hold that the incubation period is shortened in the presence of a vitamin B_1 deficiency. Bertiolotti (1936) is obviously uncertain, for he holds that degenerate and developmental forms of leprosy follow the use of diets deficient in various vitamins. Lampe *et alii* (1938), using normal and vitamin-deficient animals, repeated their mud-infection experiments and obtained negative results; this influenced them in withdrawing their previous positive results. Badger and Masunaga (1939) suggest that vitamin B_1 deficiency results in increased susceptibility, and also that calcium-deficient animals are incapable of utilizing vitamin B_1, and furthermore that such animals are deficient in some factor or factors. Later, with Wolf (1940), they suggest that a shorter incubation period follows a vitamin B_1 deficiency. Heiser (1939) makes the following statement:

> Claim is made that lice do not attack those animals well supplied, and fur animals on a B deficient diet have bad pelts, filled with lice. Some of the most primitive of insects, such as the common cockroach, require some of the B fractions for growth. So also do clothes moths and even bacteria in a test tube.

This statement to me appears inconsistent, in that if most primitive insects require the vitamin *B* complex, it is logical to conclude that lice and other ectoparasites require it also. It is now recognized that a shortage of the vitamin *B* complex—vitamin B_2—results in depilation, which by itself is a deterrent to ectoparasites. It is nevertheless admitted that a general lack of tone in the skin means coarseness of the hair—not loss—with an incidental ectoparasitic invasion. Heiser's suggestion of bacterial requirements, taken in conjunction with experimental evidence, raises an interesting point. Although invasion by arthropods occurs in normal rats, such invasions in leprous rats (naturally or experimentally infected) invariably occur when superficial lesions are prominent—that is, late in the infection period. Furthermore, superficial lesions occur in, and organisms more easily infect, animals receiving a balanced diet. Consequently, if the statement regarding lice is true, it can be concluded that the invading organisms in rat leprosy have utilized all the available *B* complex vitamins; therefore in future cultural investigations this aspect should be given more prominence. Experimentally, vitamin B_2 deficient animals were prepared for over three weeks and deprived of vitamin B_2 at intervals with the Number 7 diet of Clements (1936). Two animals, one receiving this diet and one stock animal showing depilation, gave the impression of a speeding-up of infection; this, however, was more apparent than real. Altogether thirty rats were used in these experiments.

EXPERIMENT XXI.—A rat, weighing 80 grammes, received the special diet for twenty-two days; its weight was then 68 grammes, and depilation was present. On the first and thirty-fifth days inunction with a granuloma emulsion was carried out for one hour on the scarified abdomen; the inunction was repeated with a similar emulsion, dried for one week and resuspended. On the second and fifth days loose organisms were seen in skin smears, but not afterwards; on the thirty-sixth and forty-first days loose organisms were seen in skin smears, but not afterwards. On the eighty-fourth day inunction was carried out for two hours, the fluid being allowed to dry on the non-scarified abdominal skin; infected urine was used after having stood for eight days at room temperature. On the eighty-fifth day a reaction was present, a non-inflammatory thickening of the skin with loose organisms on this day and at intervals; on the ninety-seventh day loose and intracellular organisms were found at intervals, and from the 110th to 140th day discrete papular lesions were present, and smears examined at intervals contained an increased number of intracellular organisms. The area became progressively granulomatous. On the 260th day fæces and urine both contained organisms, those in the fæces being increased in number. On the 380th day the lesion ulcerated; maferial from it contained many organisms, intracellular, solid and beaded. On the 500th day the rat was almost moribund, and was killed; generalized internal lesions were present. Organisms were found in most of the usual sites, together with plentiful invasions of the sternum, stomach, pylorus, duodenum and bulbo-urethral glands, as well as the bladder, kidney capsules and mesenteric glands. This is the first recorded invasion of the sternum, stomach, pylorus, duodenum and bulbo-urethral glands.

EXPERIMENT XXIIIA.—A stock rat, weighing 100 grammes, showed a vitamin B_2 deficiency in the form of extreme depilation. On the first and seventh days inunction of the scarified abdomen and non-scarified breast was carried out with fresh granuloma emulsion and with another emulsion resuspended after having been dried one week. On the third and eighth days loose organisms were found in skin smears, but not afterwards. On the nineteenth and twenty-fourth days inunction was carried out on both areas, under the same conditions, with fresh infected urine and with urine resuspended after having been washed and centrifuged a few times. On the twenty-fifth day a reaction was present with inflammatory thickening at the abdomen; loose organisms were found at intervals. On the thirty-seventh day inunction was carried out at both areas under the same conditions, and also on a series of cauterized holes; the material used was infected urine resuspended after having dried for one week. On the forty-fourth day the animal was inoculated subcutaneously with 0·5 cubic centimetre of freshly voided urine; the reaction was a nodule measuring 7·0 millimetres in two days, which ulcerated two days later, and ulcer washing contained loose organisms, one to ten fields. Organisms were also found on the well-washed and cleaned area of peripheral skin thickening. On the sixty-ninth day the rat was killed; no internal abnormalities were found. Organisms in fair numbers were found in breast and abdominal skin smears, the liver, the spleen, and the inguinal, axillary and cervical glands.

This experiment should be compared with Experiment XXIII in the uro-genital section.

Experiments with Combined Inoculation and Inunction.

EXPERIMENTS IV AND IVA.—Rats, small and large, were used. On the first, thirty-sixth, fifty-first, fifty-seventh and seventy-fifth days they were inoculated subcutaneously with various emulsions; reactions varied from nil to a nodule 9·0 millimetres in diameter with œdematous spread (Experiment IVA), which subsided quickly. On the fifty-seventh and ninety-first days inunction on the scarified abdomen was carried out with rabbit pus and material from a rat ulcer of long standing. On the ninety-eighth and 115th days inunction was performed with emulsion of primary rat ulcer and an old ulcer; on the ninety-ninth day both rats showed inflammatory skin thickening, which subsided in Experiment IVA and remained permanent in Experiment IV. From the 101st to the 106th day organisms were found in skin smears; a Breed count of skin serum from rat IV on the 106th day gave a result of 18,000,000 organisms per cubic centimetre. On the 108th and 110th days organisms were increasing in number, and many intracellular bacilli were present on the latter day. The abdominal area became progressively granulomatous in rat IV. On the 118th day rat IVA was killed; no internal abnormalities were found, but loose organisms were present in a smear from the abdominal

skin and in the liver, spleen, heart and kidneys. On the 218th day the lesion at the abdomen ulcerated permanently. On the 240th day organisms were found in the urine, and on the 270th day organisms were found in the fæces. On the 272nd day rat IV was moribund and was killed; extensive generalized internal lesions were found, the sternum, mesentery, omentum and digestive and uro-genital systems being included in the process.

EXPERIMENT V.—A large rat was used. On the nineteenth, fifty-second, sixtieth, seventieth, 109th, 113th and 126th days subcutaneous inoculations were made with small doses of various emulsions. Reactions occurred, the areas varying in diameter from 2·0 to 9·0 millimetres; four ulcerated, others absorbed. On the eightieth day the animal was inoculated with emulsion of *Ctenocephalides felis* which had fed on a rat granuloma; no reaction had occurred on the first, eleventh, eighty-fifth, eighty-eighth, ninety-fifth and ninety-eighth days after inoculation. Inunction was carried out with various emulsions including rat lice. Repeated examinations of skin smears revealed no organisms. On the 131st day the rat was killed; no internal lesions were found, nor organisms in skin or organs.

EXPERIMENTS K.B.—Three rats of medium size were used. On the first day they were inoculated subcutaneously at the right hind leg with organisms from a leprous wild rat stored frozen for one week. No reaction, early or late, occurred up to three months. On the ninety-first day subcutaneous inoculations were made at the left hind leg with emulsion from an old leprous ulcer of a living rat; reactions up to 9·0 millimetres in diameter were present on the third day; all were absorbed. On the 117th day rat A was inoculated subcutaneously at the higher part of the breast and the lower portion of the abdomen with untreated fæcal emulsion; reactions, up to 9·0 millimetres in diameter, were present on the second day, and had been absorbed by the seventh day. Rat B received on the scarified abdomen an inunction with fresh fæcal emulsion; rat C received an inunction with a fæcal emulsion treated for twenty-four hours with antiformin and washed. On the 118th day rats B and C showed inflammatory thickening of the skin. From the 119th to the 126th day loose organisms were found in the abdominal skin of rats B and C. On the 129th day abdominal papules were present on both rat B and rat C; on the 138th day loose organisms were found in the skin of the abdomen of both these rats. On the 145th day lesions were present in these two rats showing granulomatous tendencies. On the 153rd day an admixture of loose and intracellular organisms was present in both rats. On the 281st day organisms were present in the fæces and urine of all three rats. On the 320th day rat A was killed by the others and partially eaten; extensive lesions were present. On the 321st day rats B and C passed myriads of organisms in the fæces. On the 324th day the lesions of both rats ulcerated. On the 372nd day rat C, killed, was almost completely eaten by rat B. On the 377th day rat B, which was dying, was killed for Klotz colour fixation; a heavy generalized infection was present.

Uro-Genital Infections.

Records of organisms in the urine of rats have been previously made; but no one appears to have taken them seriously—they have merely been considered as elimination products. McCoy (1908) found them in the bladder. Berny (1934), although he failed to find bacilli in the urine on primary examination, did recover them for six days after injecting the animals with novarsenobenzol. Grall (1937) found bacilli in urine and fæces of rats, but apparently ignored the finding. Concentrating on sections of the uro-genital system, I have found pathological changes and bacilli in the bladder, kidney capsules and bulbo-urethral (Cowper's) glands, while organisms were noted in the testicles and the preputial glands. Urine, fresh, centrifuged and washed, or antiforminized and washed, inoculated subcutaneously, produced lesions up to nine millimetres in diameter, which were absorbed or ulcerated after various intervals. After storage at room temperature the urinary organisms were capable of invading the skin of rats; when resistance had been previously broken down they proceeded to an inflammatory condition when the leucocytes were mobilized and invaded by organisms. About this time lesions of a papular, nodular or granulomatous character appeared, the latter subsequently ulcerating. In the laboratory animals bacilli usually appeared in the urine about 260 days after the primary treatment.

EXPERIMENT XXIII.—The rat used weighed 100 grammes. The abdomen was scarified, but the breast was not scarified. On the first and seventh days inunction with an old ulcer washing was carried out; on the second occasion the washing was resuspended after being dry for one week. On the third and eighth days examination of skin smears revealed loose organisms, but not afterwards. On the nineteenth, twenty-fourth, thirty-seventh and forty-fourth days inunction was carried out with fresh urine, with centrifuged-washed urine with a resuspension of urine deposit which had been dry for one week, and with fresh infected urine; the last-mentioned, on the twenty-fifth day, produced inflammatory thickening of the skin, and bacilli were found at intervals. On the fiftieth day inunction with a washing of a primary ulcer was carried out. On the fifty-sixth day papular lesions and loose bacilli were noted. On the sixty-ninth day the rat was killed. Macroscopic examination revealed no internal lesions; organisms were found in the abdominal skin and papules, and also in the liver, spleen and inguinal glands.

EXPERIMENTS XIX AND XIXA.—Rats of medium size were used. The abdomen was scarified, but the breast was not scarified. On the first, sixth and ninth days inunction of both areas was carried out with primary ulcer washing, with the same again, and with rabbit pus washing; on the sixteenth day inunction of rat XIX with granuloma washing after eighteen hours' freezing and one hour at 37° C. and of rat XIXA with similar emulsion after freezing for four hours was carried out. Examination of skin smears gave negative results. On the seventy-third and 107th days inunction with granuloma washing was carried out, on the second occasion with resuspension of the washing after having been dry for one week. Examination of skin smears at intervals gave negative results. On the 118th day, inunction with fresh infected urine was carried out; examination of skin smears at intervals revealed loose organisms in both rats. On the 133rd day rat XIXA was found to have loose bacilli and a few intracellular bacilli in skin smears. On the 142nd day papular lesions were present on the abdomen of both rats, and at intervals loose and intracellular bacilli were detected; the lesions gradually coalesced to form small granulomata. On the 193rd day organisms were found in the fæces of rat XIXA. On the 240th day organisms were found in the fæces of rat XIX. On the 368th day rat XIXA was killed; no internal lesions were present, and in the breast and abdominal skin both types of bacilli were found, a few being loose in the skin of the rump and head. A fair number were also found in the lung, hind leg muscle, and inguinal, axillary and cervical glands. On the 474th day rat XIX was killed; the liver was mottled, and the spleen and inguinal glands were enlarged. The skin of the abdomen contained many loose and intracellular organisms with globi and parallel bundles; organisms were also present in the spleen, the pericardium and the inguinal, axillary and suprarenal glands, and a few were found in the brain. Neither the bladder nor the urine of either rat contained bacilli.

Digestive Tract Infections.

Lowe (1937) states that the gastro-intestinal tract is apparently unaffected, for no lesions have been reported in it. De Souza-Araujo (1938) found bacilli in the kidney and fæces; although he found the globies of Marchoux and the globi of Neisser, he apparently missed their significance. These findings made Stefansky's bacillus approach more nearly in identity to Hansen's bacillus. Grall found fæcal organisms. As has previously been pointed out, my own findings in the digestive tract suggested a new approach to the dissemination of the disease. Concentration on the problem pointed to the necessity of superinfection with organisms of a virulent character; local resistance was soon broken down by inunction with the more virulent type of organisms, but the less virulent required a variable length of time. When local resistance was broken down, either lesions or intracellular organisms appeared, in that order or *vice versa*, sometimes almost simultaneously. After each primary or secondary inunction, loose organisms appear temporarily in the skin after one of the subsequent inunctions, and clinical lesions indicating progressive disease appear; these are permanent, and according to the virulence of the organisms, may be papular, nodular or granulomatous. The two former types may be single or multiple; they frequently coalesce to form a granuloma which eventually ulcerates. The time of first appearance of organisms in the fæces varies from about 190 to 250 or more days. Experimental observations were carried out with one or all of the following fæcal

emulsions: freshly voided fæces, long-standing emulsion, after antiformin centrifuging and washing, dry fæces which had stood from a few days to many months.

EXPERIMENT XXXV.—A rat of medium size was used; the abdomen was scarified, the breast was not scarified. On the first, twentieth, forty-first, forty-sixth, fifty-seventh, sixty-seventh, eighty-first and 102nd days inunction with various emulsions was carried out. From the third to the eighty-second day skin puncture smears sometimes contained no bacilli, but mainly loose organisms were found; on the eighty-second day intracellular organisms were associated with small papular lesions. From the ninety-first to 145th day examination of skin puncture smears at intervals revealed an increase in the number of invaded leucocytes. On the 157th day the rat was killed; no internal lesions were noted, but small papules were present on the breast and abdomen, which contained numerous organisms. The skin in both places contained many organisms, which were also present in the liver, the spleen and the inguinal and axillary glands.

EXPERIMENT XXXVI.—A rat of medium size was treated as in Experiment XXXV. On the first, thirteenth, twenty-ninth, forty-second, seventy-seventh and 120th days inunction with fresh and antiforminized washed fæcal emulsions was carried out. On the fourth day, in skin puncture smears, loose organisms were found at intervals. On the forty-sixth day a few small papular lesions were noted on the abdomen; loose organisms were found in the skin at intervals. From the fifty-fifth to the 120th day, in skin smears loose and intracellular organisms were found. On the 133rd day the rat was killed; no internal lesions were found, but in the abdominal skin and papules many loose and intracellular organisms were present. Organisms were also present in the inguinal and axillary glands.

EXPERIMENTS XXXVIIIa AND XXXVIIIb.—Rats of medium size were used. Infected dry fæces were used throughout for emulsions. At the start the fæces had been dry for ten months (304 days); from the day indicated the dry age may be calculated. The abdomen was scarified, the breast was not scarified. On the first, fourth, twelfth, nineteenth, thirty-sixth, fifty-fifth, eighty-first, 161st and 183rd days inunction with emulsions of dried fæces was carried out. From the second to the thirtieth days, in skin puncture smears at intervals loose organisms were found. On the thirty-fifth day rat A showed two small papules. On the thirty-sixth day rat A showed another papule; on rat B no lesions were noted. On the fifty-eighth day the rats were chloroformed and inoculated after skin slits had been made and probing had been carried out between and to the fore and hind regions. On the sixty-third day papular lesions were found in bunches at both probed regions. On the sixty-eighth day the lesions were mostly small; one in rat B was 5·0 millimetres in diameter, and subsequently subsided. From the eightieth to the eighty-third day examination of skin puncture smears from both rats revealed loose organisms. On the ninety-fourth day skin smears of both rats at intervals were found to contain loose and intracellular organisms. On the 124th day the rats were inoculated subcutaneously with their own hæmolyzed blood. On the 127th day rat A showed a small papule and rat B showed a larger papule. On the 131st day the papule in rat A had been absorbed; in rat B the papule had increased in diameter to 2·0 millimetres. On the 134th day the blood nodule in rat A ulcerated, and in a washing loose organisms were found. On the 161st and 183rd days skin smears of both rats contained loose and intracellular organisms. On the 214th day the rats were killed. No internal lesions were noted; in rat A bacilli were found in the liver and in the axillary and cervical glands, and suspected organisms were seen in the thyreoid, the lung, the spleen and the suprarenal glands. In rat B bacilli were found in the abdominal skin, the liver, the spleen and the axillary and cervical glands, and suspected organisms were noted in the kidney, the pericardium and the bone marrow, numerous Hoffmann granules being present in the last-mentioned.

In comparison with the results of experiments in which fresh fæcal organisms were used and similar times were observed, these rats showed much lighter infections. It is probable that a generalized infection would have resulted if time had been allowed for it to develop; furthermore, in nature continuous contact with only dried organisms would not be a feature.

EXPERIMENT XXXIX.—Three medium-sized rats were used. On the first day primary inoculation by the new skin-slit-probing method was carried out, the cavity being filled with an emulsion of fresh fæcal bacilli. On the fourth day the rats showed bunches of papules and nodules up to a maximum diameter of eleven millimetres. On the seventh day the larger nodules in all the rats ulcerated, and organisms were found in washings; rat C yielded numerous organisms containing globi and parallel bacilli. On the thirty-fifth day the breast was not scarified, but the abdomen was scarified, and inunction with fresh fæcal emulsion was carried out. On the fifty-second and seventy-third days inunction with fæcal emulsion, which had stood for twenty-four hours at room temperature, was performed. On the eightieth day rat B was killed; no lesions were found, and no organisms in the axillary glands and bone marrow. On the eighty-fourth day rat A was killed; no lesions were found, and no bacilli in the liver and spleen. On the ninetieth day the leg muscle of rat C was inoculated with organisms stored for six months after chloroform extraction. On the 108th day inunction with an emulsion of dry fæces stored for 102 days was carried out. On the 121st day the same operation was carried out with fæces stored dry for 112 days and then having stood for three days at room temperature in emulsion. On the 129th day inunction with the same emulsion after it had stood in the room for eleven days was carried out. On the 163rd day rat C was killed; no internal abnormalities were detected, and no organisms were recovered from the leg muscle inoculated on the ninetieth day. Papular lesions were found in the axillary and inguinal regions and on the abdominal skin, the inguinal, axillary and cervical glands contained numerous organisms, and fewer organisms were found in the thyreoid, abdominal muscle and lung, Hoffmann granules being found in the last-mentioned.

Attempt at Infection with Fæcal Bacilli Given by Mouth.

Cannibalism in rat leprosy has long been emphasized. It has been considered that the bacilli are localized to the deeper lymph nodes. Lampe and Lobel (1938) have recorded more generalized infections. After feeding animals with infected material, Marchoux and Sorel obtained infection in 25% and Muir and Henderson (1928) 29·1%. Markianos failed to obtain infection by feeding infected lice to rats. Fite (1942) inoculated human organisms subcutaneously in a long series of rats and obtained six positive results, five with the agency of gastric mucin. Fite says nothing of the mechanism or significance of these last-mentioned results. Infection has been produced by single inoculations with granuloma bacilli; this has now also been effected by repeated skin invasions with virulent organisms from the fæces, and would probably result from persistent treatment with organisms of primary ulcers and urine; I have, however, been unable to produce clinical lesions by repeated inunction with bacilli from granulomata or from long-standing ulcers. In consequence of the consistently positive results obtained with fæcal organisms, it was considered that coprophagy might play an important role in infection. To test this, emulsions of fæcal organisms were mixed with the drinking water. Unexpectedly the results were negative; but whether this was due to the comparatively small number of organisms, to the short period of observation or to their incapacity to produce infection by this route, is uncertain. It was taken for granted that each animal would receive the same number of organisms; but it was found that heavier emulsions were objectionable, and those given took four days to drink. Fæcal examinations were made regularly, bacilli being noted only during or immediately after drinking periods. Ten rats were used and killed indiscriminately, and thirty portions of skin and organs were examined by smears.

EXPERIMENT XXXVII.—Fæces were emulsified, and the content of bacilli was estimated by Breed count; the emulsion was then added to the drinking water. In all, 12,500,000 bacilli per rat were given on the first, tenth, twenty-first, thirty-first and fifty-fifth days. On the twenty-fourth day a rat was killed at the end of the third drinking period; organisms were noted in smears from the stomach and intestine and a few in the bone marrow of hind leg. On the thirty-first day a rat was killed, seven days from the end of the third drinking period; no abnormality or organisms were detected in the organs and skin. On the fortieth day a rat was killed, five days from the end of the fourth drinking period; the organs and skin again were free from organisms. On the sixtieth day a rat was killed, one day

from the end of the fifth drinking period; a few organisms were found in the stomach, and migratory bacilli were present in the brain, testicle and axillary glands. On the sixty-seventh day a rat was killed, eight days from the end of the fifth drinking period; organisms in fair numbers were present in the stomach, and migratory bacilli were found in the spleen and in one ear. On the ninety-fourth, 104th, 135th, 164th and 174th days the remaining rats were killed, and the results of examination were completely negative.

It will be noted that organisms were found mainly in the digestive system, and scattered migratory bacilli were present in a few parts of the body. The presence of organisms was closely associated with the drinking periods, the maximum number being found eight days after the fifth period; concentration or colonization of the organisms was missing. As granuloma organisms can cause infection through the digestive tract and fæcal organisms through the skin, the results obtained in this series raises the question whether bacilli from a diseased stomach are detrimentally affected by the gastric juices of a normal animal. Periera and Anderson (1936) have pointed to the functional impairment in the stomach in human leprosy, and this suggests a similar condition in rats which requires elucidation.

Hookworm Larvæ and Rat Leprosy.

In view of the finding that the rat's stomach becomes infected (and incidentally the fæces), the consequent contamination of the soil and infection of rats through the skin with fæcal bacilli raise an interesting point—namely, whether parasitic or skin-invading worm larvæ, which have been in contact with contaminated soil, can act as infecting agents. To test this, experiments were started with the dog-cat hookworm *Ankylostoma brasiliense*; fæcal cultures were made, either alone or associated with rat fæcal organisms. The infective larvæ were collected by the Baermann apparatus.

EXPERIMENT XL.—Five rats of medium size were used. Dried fæces were made into emulsions, which in two cases were soaked on the unshaven ventral surface, first with ordinary hookworm larvæ for two hours, secondly with infected hookworm larvæ only for thirty minutes, and thirdly with an emulsion and infected hookworm larvæ again for thirty minutes. On the first day rat A was tested; hookworm larvæ only were released; some hundreds were used on each animal, and the balance were treated with an emulsion, in which the larvæ were released. Some skin thickening was present next day in all rats, and in rats A and B later ulcerative weeping lesions appeared, which healed as the thickening subsided. Rat E was killed after one hour's contact with emulsion and hookworm larvæ, for the demonstration of larvæ and organisms in sections of the skin. Examination of skin puncture smears at intervals failed to reveal organisms. On the twenty-second day a culture of hookworm fæces and fæcal organisms was mixed and allowed to develop to the infective stage; larvæ were collected by passage of the material through the Baermann apparatus. On the thirty-fourth day many thousands of infected hookworm larvæ were released alone on the skin. On the thirty-seventh day skin thickening was present in all rats. On the thirty-eighth day rats B, C and D showed heavy scaling of the skin. On the forty-second day all rats showed lesions of an ulcerative-weeping type; examination of puncture smears of these at intervals revealed numerous intracellular diplococci, but no acid-fast organisms. On the sixty-fourth day severe weeping of the lesions of rats B and D was present, but those of rats A and C were almost healed. On the sixty-fourth day rat D was killed; examination of various organs and portions of skin revealed no acid-fast bacilli. On the seventy-fifth day the balance of the rats were soaked with an emulsion of fæcal organisms, and many thousands of infected hookworm larvæ were released for thirty minutes, before the ventral surface of the animals was cleaned. On the seventy-seventh day all the rats had more heavily ulcerated lesions, and intracellular diplococci were present; smears from rat B contained typical acid-fast organisms. On the eighty-eighth day rat C showed a soft nodule, 9·0 millimetres in diameter, which gradually subsided, and from which streptococcal diplococci and typical acid-fast organisms were obtained. On the 144th day the lesions of the rats were ulcerative in varying degrees; ulceration in rat A was very slight, that in rat B consisted of a small patch at abdomen only; the abdomen of rat C was well open and weeping. On the 144th day rat C was killed; the skin was minced and passed through the Baermann apparatus, and fifteen hookworm larvæ were recovered. No organisms were noted in skin smears, but organisms were recovered in the kidney, bladder and preputial gland smears. On the 147th day rat A was killed; the skin was minced and passed through the Baermann apparatus, but only one hookworm larva was recovered. No organisms were noted in skin smears, but organisms were found in smears of the liver, spleen, lung and bone marrow, and suspected bacilli were seen in the kidney, bladder and suprarenal gland. On the 148th day rat B was killed.

No worm larvæ were recovered from the prepared skin, but organisms and Hoffmann granules were observed in abdominal skin smears. Bacilli were noted in the pericardium, the pancreas, and the axillary, cervical, preputial and suprarenal glands, while suspected organisms were found in the spleen and kidney.

The post-mortem examinations, as will be noted, were carried out early; the number of organisms in individual tissues was comparatively small, but compared favourably with the results of similar early examinations after direct invasions with fresh fæcal organisms. Since finalization of the series I have wondered whether infected larvæ only should have been used; however, if this type of infection with leprosy naturally occurs, it almost certainly takes place with externally contaminated larvæ. While the number of organisms used in experimental inunctions was in most cases known, invasion of the hookworm larvæ by organisms was an unknown quantity which could be roughly estimated by the Breed bacteria count. Consequently a culture of dog fæces with hookworm eggs and rat fæcal organisms was mixed and allowed to mature for twelve days; the worm larvæ were then passed through the Baermann apparatus. To clear off external debris and organisms the larvæ were washed several times with distilled water and then fixed with hot 70% strength alcohol. One hundred larvæ were counted and allowed to dry in a mortar; they were then ground dry with a pestle, grinding was continued with small amounts of saline solution, and each lot was collected until eleven cubic centimetres were obtained. The whole was well mixed, and Breed smears were made, fixed, stained by the Ziehl-Neelsen method and examined. The series examinations revealed an average of one organism to twenty fields, or 15,000 per cubic centimetre. Since all organisms of 100 larvæ were contained in the volume of eleven cubic centimetres, the count would be 165,000 or 1,650 per larval hookworm. I would draw attention to the fact that the larvæ penetrated the skin almost immediately they were released.

Summary.

1. The geographical distribution of leprosy in rodent species is obviously spreading as interest is centred more definitely on the problem. New findings for New South Wales are herewith recorded—namely, two specimens of *Mus musculus* and three specimens of *Rattus norvegicus*.

2. The distribution of organisms in the body of infected animals is recorded in additional sites—the stomach, pylorus, duodenum, sternum, pericardium, brain, and bulbo-urethral and preputial glands.

3. The estimated number of organisms eliminated per day in advanced cases is approximately 1,250,000,000 in the fæces; in the urine the number varies up to a maximum of 21,000,000.

4. The morphological changes in the organisms are confined to variations in the length of the bacilli, while staining inequalities are, in part at least, due to faulty technique.

5. The lepra cells associated with the superficial lesions of the rat are considered to arise from the polymorphonuclear leucocytes, the nuclear structure of which is partially or completely destroyed as the invading organisms increase in number. No digestion of organisms in these cells takes place.

6. The organisms of rat leprosy are graded in virulence; the virulence is much greater in the organisms from fæces, urine and primary ulcers than in those from granulomata and long-standing ulcers. It is suggested that by the passage of organisms from granulomata and old ulcers through guinea-pigs and rabbits the virulence may be considerably built up.

7. By superinfection at regular intervals with the more virulent type of organisms, resistance—local and general—may be broken down early; however, superinfection with less virulent organisms at irregular intervals tends to build up an immunity which may eventually destroy all signs of infection.

8. Primary clinical lesions of a temporary character are invariably produced by subcutaneous injections of emulsions containing rat leprosy organisms. In this connexion it is interesting to note that such lesions result from injections of the hæmolyzed blood of infected animals.

9. Clinical lesions of a permanent character and primary in origin may be produced by repeated inunctions with virulent organisms. The lesions appear early in laboratory animals. If metastatic lesions of rat leprosy are a feature, they occur only late in the disease.

10. Glandular infection, which may persist or disappear, is an early manifestation of the disease and may result from a single invasion of organisms through the skin. These organisms sometimes remain in the skin for considerable periods, but do not proceed to intracellularity. The musculo-cutaneous disease is a product of superinfection with more virulent organisms, producing lesions and intracellular organisms which are permanent features resulting in generalized infections. Even after the organisms have been dry for twelve to eighteen months in the fæces, infection may still be produced.

11. Vitamin B_2 deficiency in experimental rat leprosy was found to have no demonstrable influence on infection.

12. Infection of the digestive tract in rat leprosy apparently arises in the stomach and produces a progressive destruction of the mucosa from the cardiac end. Infection of the uro-genital system is particularly prominent in the bulbo-urethral (Cowper's) gland and sometimes in the preputial glands.

13. While granuloma organisms produce infection when passed through the digestive tract, fæcal organisms appear to be incapable of doing so. From this it has been deduced that the fæcal organisms from the diseased stomach are affected by the gastric juice of the normal rat stomach.

14. Infection of rats has been effected by the agency of hookworm larvæ—whether by infected larvæ direct or by organisms carried externally through the punctured skin is uncertain. It has been shown that the larvæ take up the organisms.

15. Infection has been the result of feeding rat lice, also by subcutaneous inoculation and inunction of emulsions of ectoparasites.

16. From the experiments described, the early appearance of typical clinical lesions and intracellularity of the organisms appear to settle the question of specificity of the acid-fast organisms for the disease.

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Bibliography.

S. Adler: "Human Leprosy in Syrian Hamster", *The Lancet*, Volume II, 1937, page 714.

S. Asami: "Concerning the Carrying of the Leprosy Bacillus by Insects", *La Lepro*, Volume III, 1932, page 5; cited in *International Journal of Leprosy*, Volume II, 1934, page 465.

L. F. Badger: "Leprosy", *Public Health Reports*, Volume LI, 1936, page 25.

L. F. Badger and W. H. Sabrell: "Leprosy: Effect of Vitamin B_1 Deficient Diet on Incubation Period of Rat Leprosy", *Public Health Reports*, Volume L, 1935, page 855.

L. F. Badger and E. Masunaga: "Possible Relationship of Calcium Deficiency to the Utilization of Vitamin B_1", *Public Health Reports*, Volume LIV, 1939, page 1775.

L. F. Badger, E. Masunaga and D. Wolf: "Leprosy: Vitamin B_1 Deficiency and Rat Leprosy", *Public Health Reports*, Volume LV, 1940, page 1027.

S. E. B. Balfour-Jones: "The Experimental Transmission of Rat Leprosy to the Golden Hamster", *The Journal of Pathology and Bacteriology*, Volume XLV, 1937, page 739.

P. Berny: *"La bacillurie chez les rats lépreux"*, *Bulletin de la Société de pathologie exotique*, Volume XXVII, 1934, page 910.

L. Bertiolotti: "Inoculation of Human Leprosy Tissue into Rats on Vitamin Deficient Diets", *Archivo italiano di scienze mediche coloniali*, Volume XVII, 1936, page 577; cited in *International Journal of Leprosy*, Volume VI, 1938, page 596.

Boyé: *"Sur une maladie de la sarigue de Guyane présentant de grandes analogies avec la lèpre humaine"*, *Bulletin de la Société de pathologie exotique*, Volume XXIV, 1931, page 637.

R. S. Breed: "The Determination of the Number of Bacteria in Milk by Direct Microscopic Examination", *Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Volume XXX, 1911, page 337.

E. R. Clark and E. L. Clark: "The Reaction of Cells in the Tadpole's Tail to Injected Croton Oil, as seen in the Living Animal", *The Anatomical Record*, Volume XVIII, 1920, page 227; "Changes in the Nuclei of Leucocytes in Aseptic Inflammation in the Tadpole's Tail", *ibidem*, Volume XXV, 1923, page 123.

F. W. Clements: "Tropical Ulcer, with Special Reference to its Ætiology", THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, 1936, page 615.

E. V. Cowdry: "Cytology of Leprosy", *Puerto Rico Journal of Public Health and Tropical Medicine*, Volume XIV, 1938, page 95.

S. L. Cummins, D. Davies and C. M. Ackland: "Mycobacterium Tuberculosis in Septic Tank Effluent", *Tubercle*, Volume X, 1929, page 310.

D. H. Currie and H. T. Hollman: "Further Observations on Rat Leprosy", *Lepra*, Volume XIII, 1913, page 17; quoted by Lowe, *loco citato*, 1937.

C. Cook: "The Epidemiology of Leprosy in Australia", Service Publication Number 38, 1927, Commonwealth of Australia, Department of Health.

G. Dean: "Further Observations on a Leprosy-like Disease of the Rat", *The Journal of Hygiene*, Volume V, 1905, page 99.

O. E. Denny and B. E. Eddy: "Comments on In Vitro Behaviour of Lepra and other Acid-Fast Organisms in Presence of Leucocytes", *Archives of Dermatology and Syphilology*, Volume XXVII, 1933, page 794.

E. H. Derrick: "Rat Leprosy", "Annual Report of Health and Medical Services, Queensland", 1935-6, page 29.

C. D. De Langen: "Superinfection with Leprosy", Eighth Congress (Bangkok), *Transactions of the Far Eastern Association of Tropical Medicine*, 1931; cited in *International Journal of Leprosy*, Volume I, 1933, page 220.

H. C. De Souza-Araujo: "Experimental Leprosy", *Transactions of the Royal Society of Tropical Medicine*, Volume XXIV, 1931, page 577; "The Morphology of Stefansky's Bacillus", Cairo Leprosy Conference, 1938; cited in *International Journal of Leprosy*, Volume VI, 1938, page 468.

J. W. Fielding: "The Lepromin Test in Laboratory Animals", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, 1944, page 439.

G. L. Fite: "Development of a Leprous Process in Rats, at Site of Inoculation with Material from Human Leprosy", *Public Health Reports*, Volume LVI, 1941, page 1919.

J. Francis: "Infection of Laboratory Animals with Johne's Disease and Leprosy", *Nature*, Volume CLII, 1943, page 250.

F. P. Gay: "Local Resistance and Local Immunity to Bacteria", *Physiological Reviews*, Volume IV, 1924, page 191.

A. Grail: "Blockade of the Reticuloendothelial System in Rat Leprosy", *Bulletin de la Société de pathologie exotique*, Volume XXX, 1937, page 636.

V. Heiser: "You're the Doctor", 1939, page 90.

W. H. Hoffmann: *"Los Grânulose intracellulares del virus de la lepra"*, *Revista de medicina y cirugia de la Habana*, Volume XXXIX, 1935, page 709; cited in *International Journal of Leprosy*, Volume V, 1937, page 125.

T. Ichihara: "Rat Mites (Lælaps Nezumi. Kishida, 1915): The Transmitter of Rat Leprosy", *La Lepro*, Volume VII, 1936, page 33; cited in *International Journal of Leprosy*, Volume VI, 1938, page 138.

T. Itihara: *"Studien über die Rattenlepra; Statische Beobactungen uber die Rattenlepra"*, *La Lepro*, Volume X, 1939, Supplement 95; cited in *International Journal of Leprosy*, Volume VIII, 1940, page 554.

N. A. Kingsbury: "Human Leprosy: Attempted Transmission to Rats", Annual Report of the Institute of Medical Research, Federated Malay States, 1931, page 63.

C. Krakower and L. M. Gonzalez: "Spontaneous Leprosy in a Mouse", *Science*, Volume LXXXVI, 1937, page 617; "Mouse Leprosy", *Archives of Pathology*, Volume XXX, 1940, page 308.

C. Krakower, P. Morales-Otero and J. H. Axtmayer: "The Effect of Sulfanilamide on Experimental Leprosy", *The Journal of Infectious Diseases*, Volume LXXII, 1943, page 1.

A. R. Lamb: "Effect of Malnutrition on Pathogenesis of Rat Leprosy", *The American Journal of Hygiene*, Volume XXI, 1935, page 438.

P. H. J. Lampe: *"Ratten-lepra"*, *Geneeskundig Tijdschrift voor Nederlandsche-Indie*, Volume LXXV, 1935, page 24.

P. H. J. Lampe and C. E. De Moor: *"Ratten-lepra", Geneeskundig Tijdschrift voor Nederlandsche-Indie*, Volume LXXV, 1935, pages 634 and 2033.

P. H. J. Lampe, C. E. De Moor and F. G. Van Veen: *"Ratten-lepra", Geneeskundig Tijdschrift voor Nederlandsche-Indie*, Volume LXXVI, 1936, page 2204, and Volume LXXVIII, 1938, page 523.

P. H. J. Lampe and L. W. M. Lobel: *"Ratten-lepra", Geneeskundig Tijdschrift voor Nederlandsche-Indie*, Volume LXXVIII, 1938, page 179.

M. R. Lewis: "The Formation of Macrophages, Epithelioid Cells and Giant Cells from Leucocytes in Incubated Blood", *The American Journal of Pathology*, Volume I, 1925, page 91.

J. Lowe: "Studies in Rat Leprosy", *The Indian Journal of Medical Research*, Volume XXII, 1934, page 187; "Rat Leprosy", *International Journal of Leprosy*, Volume V, 1937, page 311; "Bandicoot Infected with Stefansky's Bacillus", *International Journal of Leprosy*, Volume VII, 1939, page 75.

E. Marchoux: *"Transmission de la lèpre par les mouches", Annales de l'Institut Pasteur*, Volume XXX, 1916, page 61; "Leprosy of Rats", *International Journal of Leprosy*, Volume II, 1934, page 88.

E. Marchoux and V. Chorine: *"Transmission de la lèpre par les poux et par les Lælaps", Bulletin de la Société de pathologie exotique*, Volume XXXII, 1939, page 477.

E. Marchoux and F. Sorel: *"La lèpre des rats", Annales de l'Institut Pasteur*, Volume XXVI, 1912, page 778.

J. Markianos: *"Le rôle des poux dans la transmission de la lèpre", Bulletin de la Société de pathologie exotique*, Volume XXII, 1929, page 633.

A. A. Maximow: "Tuberculosis of Mammalian Tissue in Vitro", *The Journal of Infectious Diseases*, Volume XXXIV, 1924, page 549.

S. Mazzo: *"Fagocitosis de los bacilos de Stefansky en el peritoneo de ratas y cobayes", Prensa médica Argentina*, Volume II, 1924-5, page 879; cited by E. B. McKinley, *loco citato*.

G. W. McCoy: "Leprosy-Like Disease in Rats", *Public Health Reports*, Volume XXIII, 1908, page 23.

E. B. McKinley: "The Bacteriology of Leprosy", *International Journal of Leprosy*, Volume VII, 1939, pages 1 and 217.

E. B. McKinley and M. H. Soule: "Studies in Leprosy", *The Journal of the Americal Medical Association*, Volume XCVIII, 1932, page 361.

Metchnikoff: "Immunity in the Infectious Diseases", 1905.

E. L. Morgan: "Detection of Living Tubercle Bacilli in Septic Tank Effluent", "Report of the Director-General of Public Health, New South Wales", 1929, page 112.

E. Muir and J. M. Henderson: "Rat Leprosy", *The Indian Journal of Medical Research*, Volume XV, 1928, page 807.

J. Oliver: "The Origin of the Lepra Cells", *The Journal of Experimental Medicine*, Volume XLIII, 1926, page 233.

P. C. R. Pereira and H. H. Anderson: *"Exame do contendo gastrico de leprosos", Revista brasileira de leprologia*, Volume IV, 1936, page 145; cited in *International Journal of Leprosy*, Volume V, 1937, page 394.

F. Plantilla: "Transmission of Leprosy. I: Sites of the Single Leprotic Lesions", *Monthly Bulletin of the Bureau of Health, Manila*, Volume XVI, 1936, page 137.

R. O. Prudhomme: "Presence of Cevitamic Acid in Lesions of Murine Leprosy", *Comptes rendus des séances de la société de biologie*, Volume CXXVI, 1937, page 1004.

H. Priestley: "Rat Leprosy in North Queensland", *The Australasian Medical Gazette*, Volume XXXIV, 1913, page 405.

L. Rabinowitsch: *"Ueber eine durch saurefeste Bacterien hevorgerufene Hauterkrankung", Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Volume XXXIII, 1903, page 755.

L. Rogers and E. Muir: "Leprosy", Second Edition, 1940.

H. Sakurai: "An Experimental Study on Penetration of Lepra Bacilli", *La Lepra*, Volume VII, 1936, page 9; Volume VIII, 1937, page 491; cited in *International Journal of Leprosy*, Volume V, 1937, page 542.

J. A. Salle: "On the Cultivation of an Acid-Fast Organism from Leprous Lesions in Tissue Culture and other Media", *International Journal of Leprosy*, Volume II, 1934, page 201.

O. Schobl, E. V. Pineda and I. Miyao: "Clinical Skin Lesions in Philippine Monkeys Resulting from Experimental Inoculation with Human Leprous Material", *Philippine Journal of Science*, Volume XLI, 1930, page 233.

M. H. Soule: "The Relationship of Human and Rat Leprosy", *International Journal of Leprosy*, Volume III, 1935, page 291.

W. Stefansky: *"Eine lepra-ähnliche Erkrankung der Haut und der Lymphdrusen bei Wanderatten", Centralblatt für Bakteriologie, Parasitenkunde und Infectionskrankheiten*, Volume XXII, 1903, page 481.

M. U. Theirfelder: *"Eukele opimerkingen over hai outstaan der lepra", Geneeskundigen Tijdschrift voor Nederlandsche-Indie*, Volume LXXVI, 1936, page 2133.

F. Tidswell: "Note on a Leprosy-Like Disease in Rats", "Report of the Board of Health on Leprosy in New South Wales", 1904, page 13.

R. Van Breuseghem: *"Lèpre et sangsues", Annales de la Société belge de médecine tropicale*, Volume XVII, Number 2, 1937; cited in *International Journal of Leprosy*, Volume VI, 1938, page 268.

M. Vespoli: *"Estudo synthetico dos mais importantes factores favorecedores da infecção hanseniana e modeladores de evolução da leprose", Revista Brasileira de Leprologie*, Volume IV, 1936, page 341; cited in *International Journal of Leprosy*, Volume V, 1937, page 230.

E. L. Walker: "Some New Aspects of the Etiology and Epidemiology of Leprosy", *The Journal of Preventive Medicine*, Volume III, 1929, page 167.

E. L. Walker and M. A. Sweeney: "Identity of Human and Rat Leprosy", *The Journal of Preventive Medicine*, Volume III, 1929, page 325.

Y. Watanabe: "Experimental Studies on Animals Concerning Leprosy. Report IV. Allergy and Inoculation of Lepra Materials", *Kitasato Archives for Experimental Medicine*, Volume XII, 1935, page 355; cited in *International Journal of Leprosy*, Volume V, 1937, page 391.

N. E. Wayson and E. Masunaga: "Rat Leprosy: Observations Concerning Transmission of Infection through the Nose", *Public Health Reports*, Volume L, 1935, page 1576.

W. B. Wherry: "Further Notes on Rat Leprosy and on the Fate of Human and Rat Lepra Bacilli in Flies", *The Journal of Infectious Diseases*, Volume V, 1908, page 507; "Experiments in Vaccination against Leprosy", *ibidem*, Volume VI, 1909, page 630.

D. Yegian and L. Baesden: "Factors Affecting the Beading of the Tubercle Bacillus Stained by the Ziehl-Neelsen Technique", *The Journal of Bacteriology*, Volume XLIV, 1942, page 667.

INFILTRATION WITH "MONACRIN" (5-AMINO-ACRIDINE HYDROCHLORIDE) AS AN ALTERNATIVE TO EXCISION IN THE TREATMENT OF CONTAMINATED WOUNDS.

By FELIX ARDEN, M.D., M.R.C.P.,
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FOR some time it has been a generally accepted surgical principle that potentially contaminated wounds, provided they reach the surgeon within a few hours of being inflicted, should be excised before being sutured. This implies not only the clearing away of blood clot, dirt and foreign material, but the removal of a narrow strip from the edges of the skin, and a layer from the surface of any fat, muscle and other tissue which may be present in the wound. The object is to leave behind no damaged or potentially infected tissue, and if excision is performed early and completely this object is achieved. The wound acquires the characters of a clean surgical incision and heals by first intention.

But it does no harm even for "generally accepted surgical principles" to be reviewed from time to time. Most surgeons will agree with Ogilvie[1] that, in the case of large wounds at least, decontamination by excision is a hope rather than a certainty. Complete excision is often impossible, because nerve trunks, vascular bundles or shafts of long bones are involved and must be spared. Further, an excised wound at best has something missing. Its closure cannot be an anatomical reconstruction, but only an approximation to it, whereby structures may have to be brought together under some tension if they are to be joined at all. It is one thing to detach from the patient pieces of tissue which have already lost their blood supply; it is quite another to cut away tissue which is merely exposed. To advocate the removal of relatively healthy tissue on the grounds that it is probably harbouring bacteria is surely pessimistic counsel, justified only if no better way of meeting the threat of infection can be found.

Role of Antiseptics.

If excision is to be avoided, we must know whether it is possible, by the use of antiseptics alone, to reduce the number of contaminating organisms in a wound below the minimal infecting dose. It must be assumed that after two hours bacteria will already have penetrated a short distance into the tissues. If an antiseptic is to reach them in this situation, surface application by itself will be inadequate. Either a sufficient quantity must be retained in the wound long enough for diffusion to take place, or the antiseptic must actually be infiltrated into the tissues around the wound. The former technique has been used with sulphanilamide powder and with penicillin.

The possibility of successfully infiltrating tissues exposed to infection was suggested by Garrod[2] in 1940, on the results obtained with acridine compounds in controlling experimental infections in mice. He wrote:

> Solutions of acridine compounds can be injected interstitially without ill effect, and thorough infiltration by this means of the tissues round a small but dangerously infected wound is good treatment. It is particularly indicated for punctured wounds . . .

ILLUSTRATIONS TO THE ARTICLE BY MR. J. W. FIELDING.

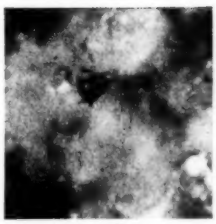

FIGURE I. — Organisms from guinea-pig nodule. (× 1,000.)

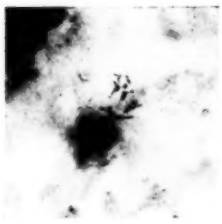

FIGURE IV. — Organisms from nodule on the 59th day showing inflammatory breakdown (× 1,000.)

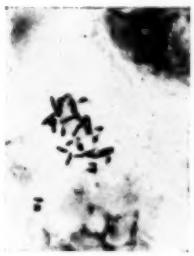

FIGURE V.—Organisms from *Polyplax spinulosus*, rat louse. (× 1,600.)

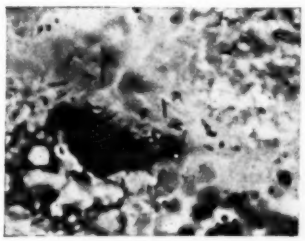

FIGURE VII.—Organisms from rat skin eight days after primary inunction. Breed count 18,000,000 per cubic centimetre. (× 1,600.)

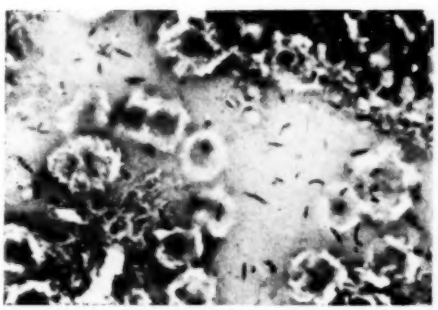

FIGURE VIII.—Organisms from rat skin ten days after primary inunction. (× 1,600.)

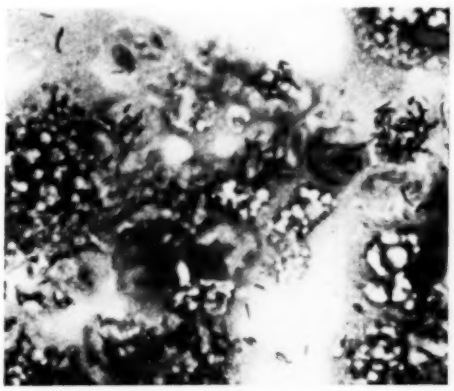

FIGURE IX.—Organisms, intracellular, from rat skin twelve days after primary inunction. (× 1,600.)

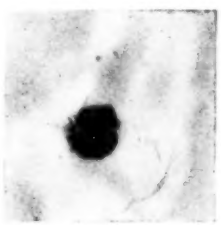

FIGURE X. — Organisms from rat skin 360th day in lymphocyte. (× 1,000.)

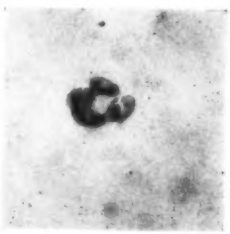

FIGURE XI. — Organism, single, in polymorphonuclear leucocyte found sixteenth day after third fæcal inunction. Human to rat series. (× 1,000.)

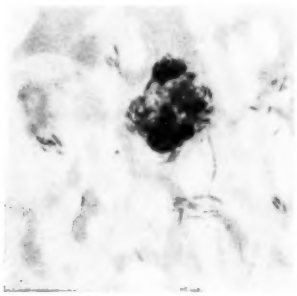

FIGURE XII.—Organisms in polymorphonuclear leucocytes from skin 360th day from original inunction. (× 1,600.)

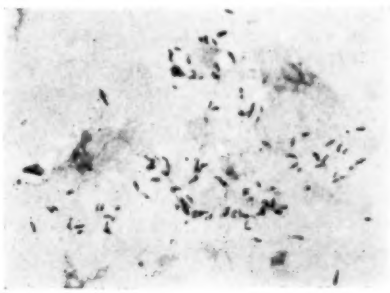

FIGURE XIV.—Organisms from ulceration at 300 days. (× 1,600.)

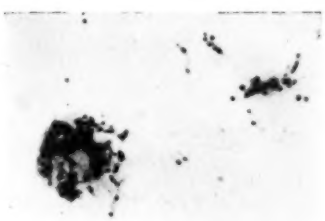

FIGURE XV.—Organisms, intracellular, from ulcer shown in Figure XIV. (× 1,600.)

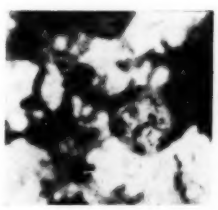

FIGURE XVIII. — Organisms in rat fæces showing globi, Hoffmann granules and bacilli of variable length. (× 1,000.)

CASE XI.—S.P., aged one year, fell and cut his forehead. There was a laceration one inch long, the periosteum being exposed. The interval before treatment was three hours. The wound healed by first intention.

CASE XII.—S.W., aged six years, sustained a compound fracture of both bones of the forearm and a puncture wound over the site of the fracture in the ulna. The interval before treatment was four hours. The wound healed by first intention.

CASE XIII.—G.S., aged ten years, was involved in a street accident. There was an irregular, three-inch laceration over the knee joint, extending through the lateral patellar retinacula and opening widely the bursa deep to the quadriceps. The skin edges were damaged with gravel. The interval before treatment was four and a half hours. The wound was inspected after eight days; the wound was partly healed, but damaged skin edges were sloughing, and fluid was present in the knee joint. Attempted culture from the sloughing edges and from the synovial fluid yielded no growth of microorganisms.

CASE XIV.—J.A., aged nine years, was involved in a street accident. The distal phalanx of the great toe was almost severed. The interval before treatment was four hours. Amputation was completed and the flaps were sutured. The wound healed by first intention.

CASE XV.—B.J., aged six years, was involved in a street accident. There was a curved laceration four inches long across the dorsum of the foot, the tendons being exposed. The skin flap was reflected downwards and contused. The interval before treatment was four and a half hours. The wound was inspected after seven days; the central portion of the distal skin flap was sloughing, and slight serous exudation was present. The remainder of the wound healed by first intention. Attempted culture from the serous exudate yielded no growth of microorganisms.

CASE XVI.—G.Z., aged seven years, had his foot caught in a bicycle wheel. There was a laceration six inches long extending from the heel, across the fibula and forward over the dorsum of the foot. The capsule of the ankle joint was opened and cancellous tissue of cuboid bone was exposed. A large skin flap was reflected downwards. The interval before treatment was five hours. The wound was inspected after eight days. The central portion of the distal flap was undergoing dry necrosis. First intention healing occurred at both ends of the suture line.

Comment.

Recorded above are brief notes of every child whose injuries have been treated by the method of "Monacrin" infiltration already described. All these children were patients of the Brisbane Children's Hospital between August, 1944, and January, 1945. Although it is not very comprehensive, in that most of the injuries involved the lower limb, the series includes four cases of open fracture, two others in which amputation was required, and three other cases in which joints had been laid open. Several of the lacerations involved muscle, and in one instance brain substance was protruding and damaged. All the wounds were potentially contaminated.

In only one of these sixteen cases (Case V) did any infection develop; *Bacillus pyocyaneus* was the offending organism. Of the remainder, healing by first intention was not possible in one (Case III), because a good deal of skin had been torn off the foot. After treatment this wound was not inspected until the fourteenth day, when attempted culture from the granulating surface yielded no growth of microorganisms.

In three other cases aseptic sloughing of the skin occurred. In one instance (Case XIII) the skin had been badly damaged by gravel, and in the other two (Cases XV and XVI) the sloughing portions represented the apices of inverted U-shaped flaps with distal pedicles. In two of these wounds a little serous ooze was found beneath the necrotic tissue when the wounds were inspected on the eighth day; but in both cases attempted culture yielded no growth. The slough in the third wound (Case XVI) was leathery and dry. In no instance was there any redness, discharge or other evidence of inflammatory reaction. As this type of aseptic sloughing is not dangerous, it seems reasonable, when dealing with doubtful skin flaps, to give them credit for being viable rather than to sacrifice them.

The wounds of the remaining eleven children healed cleanly by first intention.

It will be observed that in five of the sixteen cases the interval before treatment was commenced was longer than six hours; that is to say, the time limit generally regarded as safe for excision and primary suture had been exceeded.

Neither on pharmacological grounds nor on the experience gained from these cases does there appear to be any risk of systemic poisoning or of local damage from the interstitial use of 1 in 1,000 "Monacrin" solution. These children showed no systemic disturbance whatever, nor did they complain of more pain than the nature of the injury would lead one to expect.

This small investigation has been purely clinical. No attempt has been made to determine how long a bacteriostatic concentration of "Monacrin" remains in the vicinity of the wound after the injection of a 1 in 1,000 solution. Nor is it yet clear how much of the credit for the freedom from infection should be given to the locally injected "Monacrin" and how much to the sulphadiazine or penicillin administered systemically. These matters need to be determined.

In the meantime it is my contention that infiltration of the surroundings of a contaminated wound with "Monacrin" solution compares favourably with excision, in that it avoids the sacrifice of tissue and is yet safe enough to permit primary suture with expectation of healing by first intention. This is demonstrated in the small series of cases here reported. The method appears to merit further trial.

Summary.

The role of antiseptics in the treatment of contaminated wounds is discussed, and a method involving infiltration with 1 in 1,000 "Monacrin" solution is described.

Of sixteen wounds so treated, in one *Bacillus pyocyaneus* infection developed, one could not be closed because of skin loss, but remained sterile, in three some aseptic necrosis of skin resulted from the nature of the accident, and the remaining eleven healed by first intention.

References.

(1) W. H. Ogilvie: "Surgery of Infected Wounds", *The Lancet*, Volume I, 1940, page 935.
(2) L. P. Garrod: "Action of Antiseptics on Wounds", *The Lancet*, Volume I, 1940, pages 798 and 845.
(3) S. D. Rubbo, A. Albert and M. Maxwell: "Influence of Chemical Constitution on Antiseptic Activity: Study of Monoaminoacridines", *The British Journal of Experimental Pathology*, Volume XXIII, 1942, page 69.
(4) J. McIntosh and F. R. Selbie: "Chemotherapeutic Drugs in Anaerobic Infections of Wounds", *The Lancet*, Volume I, 1943, page 793.
(5) D. S. Russell and M. A. Falconer: "Acridine Antiseptics: Further Experiments on their Local Action", *The Lancet*, Volume I, 1943, page 580.

Reports of Cases.

A CASE OF HURLER'S DISEASE (LIPOCHONDRODYSTROPHY).

By H. R. SEAR AND J. K. MADDOX,
Sydney.

AMONG the grim faults of human development, there can be few more repugnant than the group of infantile reticuloendothelioses, which produce skeletal deformities in association with imbecility. When such a tragedy can occur twice in succession to the same parents and on each occasion transform a seemingly normal baby into a hideous, mindless caricature within twelve months, one realizes to what amazing lengths Nature's mistakes can sometimes extend.

This ghastly transmutation was first described as a separate entity by Gertrud Hurler in 1919. Although Hunter showed two brothers so affected to the Royal Society of Medicine in 1917, he failed to define the syndrome or describe the characteristic opacity of the cornea. About fifty cases have since been reported.

The basic description is now that of a kyphotic dwarf with an abnormally large and distorted head, a grotesque facies, bilateral corneal opacities, hepatosplenomegaly and mental retardation. Actually corneal clouding is absent in about 25% of the patients, and certain radiographic appearances in the skeleton are required to confirm the diagnosis. The largest English series (seven cases) was reported in full by Ellis, Sheldon and Capon in 1936; to these authors the facial characteristics suggested the features of gargoyles. Thus arose the secondary title of "gargoylism", a less desirable if more picturesque term than lipochondrodystrophy, which is more accurately descriptive. The British authors, in their text-book on X-ray diagnosis, in dealing with chondro-osteodystrophy, make the following statements:

> Gargoylism appears to be an allied disease, in that bone changes identical with chondro-osteodystrophy are encountered. It was first described by Hurler, and is referred to as chondro-osteodystrophy of the Hurler type, but the name "gargoylism", which is more commonly used, well describes the large head and grotesque faces of the children affected.

From this we beg to differ. A gargoyle is defined in the "Oxford English Dictionary" as "a grotesque spout, representing some animal or human figure, projecting from the gutter of a building in order to carry the rain water clear of the wall". It refers to deformity only, and craniostenosis *per se* may give the appearance of a gargoyle. This name conveys no reference to the underlying pathological process in the reticulo-endothelial system, and therefore is unsatisfactory. For that reason we urge that it should not be applied to this entity, and advocate the name Hurler's disease or lipochondrodystrophy. A few authors, following Engel, name the syndrome *"dysostosis multiplex"*, again in a less specific terminology. Ashby, Stewart and Watkins, in a comprehensive philosophical description, established a convincing orientation with other known lipoidoses of childhood. Individual case reports are too numerous to mention in detail, but those which also include reviews of the literature are those of Cordes and Hogan, Harvey, Lurie and Levy. We believe the following is the first case to be reported in Australia.

Clinical Record.

C.R., a female infant, was first examined at the age of nineteen months in November, 1942, at the request of Dr. Arnold Bryant, of Parramatta, who stated that she looked like a cretin or a mongol. The child was the second offspring of two cousins. The parents were ignorant of any history of mental or physical abnormality in either family, and were certain that no dwarfism had occurred among their relatives or their offspring. Their elder child at four years was apparently normal in development and appearance. The younger child had been born when the mother was thirty-six years old, and the labour had been prolonged as the result of a breech presentation. Almost from birth something had been noticed to be wrong with the feet, which was called "talipes", and it was also noted that the child snuffled continuously. Breast feeding was persisted with and progress was satisfactory until the age of one year. Certainly the teeth were rather slow in growth. The first tooth appeared at the age of nine months. At this stage the baby was contented, seemingly healthy and well nourished. Up to the age of one year no suspicion was aroused in the minds of the parents that their child was in any way abnormal, except for the varus tendency of the feet and the fact that she seemed to snuffle considerably (Figure I).

From the age of twelve months, however, this baby began to deviate increasingly from the normal course of development followed by her elder sister. Her neck seemed to shrink so that her head sat directly upon her shoulders, her forehead enlarged, her eyes became "steamy", her back humped and her abdomen protuberant. Teeth of inferior quality presented at slow, irregular intervals. By the age of eighteen months she had not walked, and was so clumsy that she could barely stand. She made grunting, inarticulate sounds, among which the words "mum" and "dad" could sometimes be distinguished.

On physical examination, at the age of nineteen months, the child appeared superficially cretinoid, but contented, and even slightly interested in her surroundings. She appeared to see large objects and individuals. In form she was fat, squat and ugly. Breathing was by mouth, interrupted by some snuffling. The forehead was overhanging and high, with obvious frontal and parietal bossing. The anterior fontanelle was widely open. The eyes were large, not proptosed, but set wide apart. The root of the nose was sunken. The nose was flat like that of an aboriginal, and the anterior nares were flared. The mouth was large and the lips appeared to be negroid or thickened. Both corneæ were equally hazy, of a ground-glass appearance. The hair was thick and fine in texture. The ears were set low, almost on the shoulders. The neck was not to be seen. The incisor teeth were peg-shaped and separated.

FIGURE I.

Normal head and facies at the age of six months.

The arms were short; flexion at wrists and elbows was limited so that on downward extension the wrist came only to the iliac crest. The forearms were thick and stumpy and the hands spatulate, with incurving of the fifth digits. A pronounced lumbar kyphosis was offset by a prominent

FIGURE II.

Showing characteristic upper extremities, and surface markings denoting enlargement of liver and spleen, umbilical hernia.

"pot belly" surmounted by a reducible umbilical hernia. Palpation through the slack abdominal wall readily revealed a uniform and firm enlargement of both liver and spleen (Figure II).

The child was admitted to the Royal Prince Alfred Hospital, Sydney, where radiographs of skull, wrists and knees were taken. One of us (H.R.S.) reported on these as follows:

> Ossific centres of two carpal bones present, also second, third and fourth metacarpals, and of internal cuneiform. The bone age would appear to be three years or slightly over. Long bones somewhat more expanded than usual; especially radii and ulnæ. There is very definite deformity of lower ends of radii and ulnæ, also wedging of bases of second, third and fourth metacarpals. These changes are associated with definite alteration in trabeculation of bone, which is looser in character than usual. This is well seen in the metacarpals and in the bones of the forearm. There is no gross change in the hip joints. The skull is scaphocephalic in type, the *sella turcica* slightly bigger than usual. There is delay in closing of anterior fontanelles. There is a suggestion of stretching of the coronal suture. There is no widening of the sagittal or lambdoid sutures. The changes in the long bones are typical of an endocrine disturbance. The shape and texture of the long bones are compatible with cretinism; but the shape of the skull and the bone age and the condition of sagittal and lambdoid sutures is against cretinism. It may be a case of atypical cretinism, but is more likely due to some pituitary dysfunction.

A series of laboratory investigations were carried out. The blood failed to react to the Wassermann test. The calcium content of the blood was 13·7 milligrammes *per centum*, the phosphorus content 1·7 milligrammes *per centum*, and the cholesterol content 272 milligrammes *per centum*. Dr. E. V. W. Pockley reported that in both corneæ haziness of the *substantia propria* was present. A blood count revealed a secondary anæmia; the red cells numbered 2,980,000 per cubic millimetre, the hæmoglobin value was 9·6 grammes *per centum* (66% of normal), and anisocytosis and polychromasia were present. The white cells numbered 6,850 per cubic millimetre; 46% were neutrophile cells, 45% were lymphocytes, 8% were monocytes and 0·5% were basophile cells. This deficiency was corrected by the administration of iron salts. After eighteen days' administration of vitamin *D* in the form of irradiated ergosterol (1,000 units per day), the blood calcium content was 12 milligrammes *per centum* and the inorganic phosphorus content of the serum was 4·3 milligrammes *per centum*.

Some adenoid tissue was detected in the post-nasal space, which was to be removed, had the child at this period not developed pertussis. She overcame this infection satisfactorily with the aid of Phase I pertussis vaccine. The adenoid tissue was removed, and she was discharged after instructions to the mother to persist with the administration of thyreoid gland (1/10 grain twice a day) and a daily supplement to her diet of 800 units of synthetic vitamin *D*. An unfavourable prognosis was decided upon, and a tentative diagnosis was given of mental deficiency, possibly associated with a lipoid reticulo-endotheliosis.

The patient was not seen again for ten months. During this time, following discussion by us and the procurement of further radiographs of the whole skeleton, the correct diagnosis was formulated. She returned at the age of two and a half years because the parents had become concerned at the increase in size of her skull and at her further general retardation. She was still unable to walk, but she could stand in a forward flexed posture and often attempted to make her first steps. She ate well and was contented in temperament. She was speechless, and never attempted to repeat any word addressed to her. From this fact, and because of her failure to react to loud noise, she was considered to be deaf. She appeared to be able to recognize familiar faces, but made no attempt to play with toys. Her sight was apparently fairly satisfactory. She weighed 26 pounds. It was obvious at a casual glance that she was now an advanced hydrocephalic (Figures IIIA and IIIB). The brow was now so prominent as to overhang the face in a grotesque protuberance. The parietal bossing was dislocated to a plane posterior to that of the ears, and the back of the skull was flat and broad. Islands of bone floated in cystic areas which represented the grossly enlarged fontanelles and widely separated coronal and lambdoidal sutures. The remaining contributions to her revolting facies were more exaggerated than ever, and highly characteristic of the published descriptions of Hurler's disease.

She reentered hospital six weeks later for further study, when Figures IIIA and IIIB were obtained. The hepatolienal enlargement was even more pronounced, opacities now covered the entire corneæ, and the short stumpy characteristics of the forearms with imperfect joint movement were more noticeable. The following skull measurements were obtained at this juncture: coronal measurement (intermeatal), 14 inches (35·5 centimetres); nasion to vertex, 10 inches (25·3 centimetres); horizontal maximum circumference, 23·5 inches (59·5 centimetres); nasion to inion, 17 inches (43 centimetres); nasion to centre of anterior fontanelle, 8·0 inches (20 centimetres). The blood calcium content was 10·9 milligrammes *per centum*, the blood cholesterol content 109 milligrammes *per centum*, the serum phosphatase content four milligrammes *per centum*, and the serum lipoid content 50 milligrammes *per centum*.

At this time she developed an upper respiratory infection, the onset of which was characterized by a series of general epileptiform convulsions which nearly caused her death. She recovered completely, however, and still remains under periodic observation.

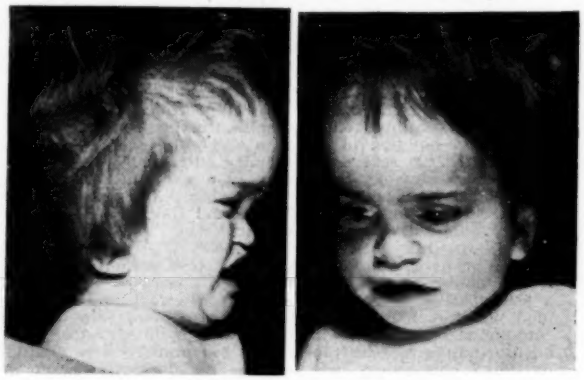

FIGURE IIIA. FIGURE IIIB.

View of skull deformities. Note the absence of neck and steamy corneæ.

Commentary.

The condition apparently tends to exteriorize about the end of the first year of life, although a few subjects appear to have some of the skeletal stigmata at birth. Slowly but surely the skull begins to become enlarged and distorted; the teeth are late in appearing and are poorly formed or peg-shaped in type. The belly protrudes, this protrusion being accentuated by a lower dorsal kyphosis and by abdominal visceral tumescence. Umbilical and perhaps inguinal herniæ then appear. This is followed by relative recession of the root of the nose, which is soon flattened, with the splaying of the nostrils accentuating the thickened lips and overhanging forehead. Further enlargement of the skull upwards and anteriorly leaves the ears set low, like those of a gargoyle. There is poor development of the cervical part of the spine, its angulation obliterating the neck so that the overgrown head appears to sit directly on the child's shoulders. The forearms become short and stubby and the hand is trident-like, with incurving of the fifth digits. A symmetrical haze is noticeable in the cornea, mental development is arrested, dwarfism becomes established and deafness finally appears.

The fully developed "gargoyle" is placid, speechless, deaf and semi-blind. Movement at elbows, wrists, fingers, shoulders and hips is limited in degree. The steamy appearance of the corneæ, which is visible in eyes set wide apart, is most striking. The towering skull is always scaphocephalic, frequently hydrocephalic, with widely separated sutures. The ears are low and obliquely placed. The mandible is usually under-developed in comparison with the maxilla. Spaces are visible between the badly formed or notched incisor teeth. The hair is fine, straight and silky in texture; the eyebrows are coarse. The thoracic cage is usually deformed, with funnel-breast or Harrison's sulcus, and surmounted by short massive clavicles. Inability fully to extend the finger phalanges results in a permanent claw hand. Walking is difficult or impossible, and many children give up the attempt. If not, the gait has a characteristic waddling character. Besides the limiting range of hip movement, dorsilumbar kyphosis is never absent, nor stunting of the cervical spine, eliminating the neck. Umbilical or inguinal hernia, or both, is constantly present, together with a smooth, firm and uniform enlargement of both liver and spleen. Mental development is arrested or greatly retarded, partly because of diminution of vision and hearing,

and partly in all probability from organic interference with cerebral function. In children who develop the disease after the age of four years more intelligence is apparent, and habits are cleanly.

All the cardinal clinical signs (cloudy corneæ, hepatosplenomegaly, herniæ, hydrocephalus) do not occur in every case. As frequently happens in examples of congenital metabolic anomalies, "link" cases with other lipoidoses and chondrodystrophies have been described. The absence of one corner stone should not allow an otherwise well-constructed clinical diagnosis to fall to the ground.

Apart from the naming of this condition "the fifth lipoid disease", nothing is known as to its ultimate origins. Its beginnings must be linked with the causes of congenital deformities in general, as these frequently coexist—for example, herniæ, *spina bifida et cetera*—or more closely with developmental functional anomalies of a biochemical character, resulting in universal lipoid accumulation either directly or perhaps through the mediation of a ductless gland. Washington is of the opinion that the skeletal changes are inexplicable on the basis of deranged lipoid metabolism, and has postulated that the sphenoid maldevelopment is the primary fault which in turn affects pituitary function, disturbing cartilage and bone growth, so allowing stress to modify the spine and long bones abnormally.

From the genetic standpoint, the syndrome frequently occurs in siblings. Thus of the fifty recorded cases, in eleven families two siblings were affected, and in four families three siblings were affected. In spite of this strong familial tendency there is usually no history of its previous occurrence in such a family. Consanguinity of parents, while existing in the present case, is exceptional. No racial or geographic limitations have been observed.

Results of four post-mortem examinations are available, including Tuthill's autopsy on one of Hurler's patients. Most attention has been devoted to the cranial contents, in which cortical atrophy and thinning, with dilated ventricles, has been the rule. The macroscopic appearance of the pituitary gland suggests that the enlarged *sella turcica* is the result of sphenoid maldevelopment rather than pituitary overgrowth. Granular lipoid is noted in and around nerve cells of the brain stem cortex and basal ganglia (the *globus pallidus*, the reticulate zone of the *substantia nigra* and the dentate nucleus of the cerebellum—the usual sites in heredomacular degeneration). The same lipoid granules have been seen in life through the slit lamp, and after autopsy, in the deeper layers of the cornea adjacent to and sometimes displacing Bowman's capsule. The liver and spleen are packed with lipoids, the nature of which has not been finally decided upon. Suggestions are that it is probably a cerebroside, phrenosin or kerasin or both, or a protein-lipoid combination.

No constant changes have been described in the endocrine glands. A general hyperplasia of non-specific character is usual in the pituitary and thymus glands. Further autopsy reports are desired, as some clinical appearances suggest glandular dyscrasia, and the entire lipoid machinery is probably a function of the pituitary-hypothalamic apparatus.

No abnormalities detectable by laboratory investigations may be relied upon to assist in diagnosis or prognosis. The blood lipoid level is not raised, and the level of plasma cholesterol is variable. The serum calcium, phosphorus and phosphatase contents are usually within the normal range. In the present case calcium and phosphorus figures were at first in the rhachitic zone, but recovered after adequate vitamin *D* therapy. In one of Ellis's cases the creatine and creatinine output was subnormal. In another case a dextrose tolerance test produced results well within accepted limits. There is no disturbance of the cellular constituents of the capillary blood. In a sternal marrow film described by Cordes and Hogan, azurophilic and basophilic granules were seen in polymorphonuclear cells at all stages of development. Defective liver function was demonstrated in one case, while liver puncture has provided histological material containing cells stuffed with lipoid. An encephalogram obtained from one patient revealed ventricular dilatation; an electroencephalogram in another case showed normal cerebral rhythm.

Radiological Findings.

Radiological findings provide the most satisfactory diagnostic criteria. In the case under review they are as follows.

The Skull.—There is considerable scaphocephalic deformity. The postero-anterior film shows obliteration of the sagittal suture, the skull condition being primarily a craniostenosis of the scaphocephalic type. The coronal suture is "stretched", this appearance suggesting some hydrocephalus as well. This view is supported by the lengthening, in the sagittal plane, of the *sella turcica*. Diploic vein markings are unusually prominent in the anterior and lower part of the frontal bone, a common feature in Hurler's disease. The suture between the basisphenoid and the basi-occipital bone is patent, as is usual in craniostenosis.

The Spine.—Kyphosis is present near the thoracico-lumbar junction, with slight deformity of the bodies of the twelfth thoracic and first lumbar vertebræ. These changes are not pronounced as is usual in osteochondrodystrophy.

The Pelvis.—The acetabula are unusually shallow, a finding common in osteochondrodystrophy, but there are no unusual changes in the epiphyses of the femoral heads or in the femoral necks, as are frequent in osteochondrodystrophy.

The Long Bones.—A slight bilateral deformity is present on the medial aspect of the humeri, there being a slight concavity of the medial aspect of the shaft towards the upper ends of the diaphyses; these are not unlike, but not so pronounced as, the changes that may be seen in renal rickets of the "white ant eaten" type. The changes in the radii, the ulnæ and the bones of the hands are more pronounced than in any of the other long bones. The radii and ulnæ are shorter than normal, somewhat wider and expanded, with curious almost cupped lower ends to the diaphyses, and the trabeculation is looser in character and the cortex possibly slightly thinned. Similar changes in the architecture of the bones can be seen in the metacarpals and phalanges; the metacarpals are somewhat shortened and the bases of some of the metacarpals somewhat wedged. The estimated radiological bone age is about three years—that is, somewhat more than the bone age of the child. It was the appearance in the architecture and trabeculation of these bones that suggested the changes in Gaucher's disease, and warned us that we were probably dealing with a reticuloendotheliosis as well as craniostenosis associated with slight osteochondrodystrophy, the combined picture being that of Hurler's disease. The gross changes in the femora and tibiæ are much less pronounced than in the bones of the upper extremity, and the tarsal bones and metatarsals show the looser trabeculation to a lesser degree than the corresponding bones in the wrist and hand.

Differential Diagnosis and Relationship to other Lipoidoses.

Clinically a distinction must be drawn between (*a*) disorders which produce dwarfism and facial distortion, (*b*) disorders which produce chondrodystrophy or osteodystrophy, and (*c*) other lipoidoses. A superficial resemblance to mongolism and cretinism is soon dispelled by a more detailed inspection of the eyes, skull and skin. Advanced rickets may simulate Hurler's disease by producing skull bossing, kyphosis, "pot belly", visceral enlargement and inferior teeth. In the case now recorded, this explanation was at one stage under serious consideration, the cloudy corneæ being ascribed to a coexistent vitamin *A* lack. Cloudy corneæ, skull bossing, snuffles, liver and splenic increase, defective dentition—all these occur in congenital syphilis, but in only one case in the literature has the blood reacted to the Wassermann test.

X-Ray Diagnosis from other forms of Skeletal Dystrophy.—The differential diagnosis from the radiological standpoint is between the following conditions:

1. Chondro-osteodystrophy. Craniostenosis has been reported in osteochrondrodystrophy and in the allied lesion achondroplasia, but the clinical picture, with the mental retardation, differs considerably from Morquio's disease.
2. Gaucher's Disease. The loose trabeculation of some of the bones is similar to the change that may be seen in Gaucher's disease; but the presence of craniostenosis is against this, and the changes in the spine and the dwarfing do not suggest it.
3. Renal Rickets of the White Ant Eaten Type. The deformity on the inner aspect of the upper ends of the humeri is similar to the white ant eaten type of deformity of renal rickets; but the child is unusually young for renal rickets, and the skull and spinal changes in no way resemble those of renal rickets.
4. Cretinism or Allied Endocrine Disturbance. In these conditions one would not expect craniostenosis and delay would occur in the appearance of the ossific centres.

Craniostenosis, mild deformities like osteochondrodystrophy, and the looser, abnormal trabeculation are all found in Hurler's disease, a lesion affecting not only the bones, but also the reticuloendothelial system. The changes in the eyes supported this view. The closest disturbance in skeletal growth is known as Morquio's disease, in which the primary fault lies in development of bones laid down in cartilage—a familial, sex-linked disorder with no skull or corneal involvement and preservation of normal mentality.

Other Lipoidoses.—A most fascinating orientation of this disorder with other well-known errors of lipoid metabolism—the so-called juvenile reticulo-endotheliosses or heredo-degenerative lipoidoses—has been achieved most successfully by Ashby, Stewart and Watkins. The original article should be consulted by all who admire a logical and philosophical discussion in the best English manner. The same histological appearances with regard to nerve cells and lipoid disposition occur in Hurler's disease as in Tay-Sach's disease (amaurotic family idiocy). In the words of Ashby *et alii*, "Amaurotic idiocy, far from being an isolated, if interesting, disturbance of lipoid metabolism, is in reality only a variant of a general lipoid degeneration, of which there are a number of different clinical types"—depending on the system most seriously deranged, and on the particular lipoid which accumulates. In the Tay-Sach syndrome, the central nervous system suffers most heavily, in Gaucher's and Niemann-Pick's disease the abdominal viscera are the chief victims, in the Hand-Schüler-Christian syndrome the entire organism suffers. Foam cells crowded with lipoid and a cherry-red spot in the macula of the optic fundus may occur in all these conditions. Hence Hurler's disease has been referred to as the "fifth lipoidosis". Four clinical links further bind these strange disorders together: a latent period of apparent good health beforehand, enlargement of liver and spleen, the presence or later development of endocrine dyscrasias, the appearance of osseous lesions and deformities. The basic distortion of the lipoid metabolic pattern seems to be the same in each, and its consequences may affect all tissues to a varying degree, resulting in many clinical and X-ray types.

Prognosis.

The outlook, fortunately, is highly unfavourable. Sufferers are prone to respiratory infection, which carries them off in early or mid-childhood. A few less affected subjects have lived twenty years. Optic atrophy and complete deafness may ultimately develop, while sexual infantilism is the rule.

Conclusion.

Much more information is needed before the vagaries of lipoid metabolism and its control will be fully understood. It is in order to prevent medical men from overlooking clinical material which may be useful in this elucidation that this case is reported.

Summary.

1. An extreme case of lipochondrodystrophy in a female child, aged twe years, is described from both clinical and radiological points of view.

2. Consanguinity of the parents was present, but is not considered a factor. The only sibling is normal.

Bibliography.

G. Hurler: "*Ueber einen Typ multipler Abartungen vorwiegend am Skelettsystem*", *Zeitschrift für Kinderheilkunde*, Volume XXIV, 1919, page 220.

G. Hunter: "A Rare Disease in Two Brothers", *Proceedings of the Royal Society of Medicine*, Volume X, 1917, page 104.

E. A. Cockayne: "Hepatosplenomegaly Associated with Mental Deficiency and Bone Changes", *Proceedings of the Royal Society of Medicine*, Volume XXVIII, 1935, page 1067.

R. W. B. Ellis, W. Sheldon and N. B. Capon: "Gargoylism (Chondo-osteodystrophy, Corneal Opacities, Hepatosplenomegaly and Mental Deficiency)", *The Quartely Journal of Medicine*, Volume V, 1936, page 119.

W. R. Ashby, R. M. Stewart and J. H. Watkins: "Chondro-osteodystrophy of the Hurler Type (Gargoylism): A Pathological Study", *Brain*, Volume LX, 1937, page 149.

J. A. Washington: Writing in Brennemann's "Practice of Pædiatrics", 1937, Chapter XXX.

D. Engel: "Dysostosis Multiplex: Report of Two Cases", *Archives of Disease in Childhood*, Volume XIV, 1939, page 217.

J. L. Henderson: "Gargoylism: Review of Principal Features with Reports of Five Cases", *Archives of Disease in Childhood*, Volume XV, 1940, page 201.

R. M. Harvey: "Hurler-Pfaundler Syndrome (Gargoylism)", *American Journal of Roentgenology*, Volume XLVIII, November, 1942, page 732.

F. C. Cordes and M. J. Hogan: "Dysostosis Multiplex: Report of Ocular Findings in Five Cases, with Review of Literature", *Archives of Ophthalmology*, Volume XXVII, April, 1942, page 637.

L. A. Lurie and S. Levy: "Gargoylism: Review of Literature with Report of Two Cases", *The American Journal of the Medical Sciences*, Volume CCVII, February, 1944, page 184.

Reviews.

A YEAR BOOK OF SURGERY.

"THE 1944 YEAR BOOK OF GENERAL SURGERY" has been published and Evarts A. Graham is once more the editor.[1] It is an interesting volume and should be useful. In his introduction Graham states that there is little new to record because the experimental laboratories have scarcely been able to function as a result of the war. He wonders how soon they will resume their former activities, and what will be the effect on them of the disruption caused by years of war, and what kind of financial support they will receive. These are questions which are exercising the minds of many teachers and investigators in medicine. For all that, Graham shows in the pages of his volume that surgeons have not been idle, and that if no epoch-making discoveries or advances can be claimed, there is still a good deal that should engage the attention of all who practise the art of surgery.

In the section on anæsthesia and analgesia there is a lengthy reference to refrigeration anæsthesia. Contributions by V. Richards and F. M. Allen and L. W. Grossman are abstracted at some length. The editor describes the contribution of the second group of authors as interesting and important. He states that the experimental work of Brooks and Duncan together with the work of Allen and his associates constitutes an important contribution to the treatment of conditions of impaired circulation. Though the older idea of applying heat to an extremity with a compromised circulation has been properly banished, he thinks that there is much to be learned about the possible harmful effects of refrigeration on nerves and perhaps on other tissues before its use can be regarded as entirely free from danger. In the section on operative technique attention is drawn to the serious effects of the introduction of talcum powder into the abdomen. Even meticulous care in washing off the surface of rubber gloves before operation does not guarantee against contamination of the operative field with talc. Talc sets up a granulomatous foreign body reaction. Potassium bitartrate is recommended as a suitable substitute for talc. In the section on military surgery reference is made to blast injuries and to burns and to high altitude frost bite. The paper by Ross and Ryan on gas gangrene at an Australian general hospital is abstracted. In regard to wound healing it is shown that the early enthusiasm for the local use of sulphonamides in the prevention of wound infection must be tempered somewhat. Reference is made to the work of certain Russian investigators into the use of phytoncides in the treatment of infected wounds. It was found that their vapours emanating from a freshly prepared onion or garlic paste are lethal to bacterial cultures. The editor remarks that it would require a large amount of intestinal fortitude on the part of many American patients to withstand the aroma of a garlic paste. Several pages are devoted to recent work on shock. Burns are also dealt with extensively under the heading of wound healing. In the section on blood vessels reference is made to a case in which occlusion of an infected patent *ductus arteriosus* was obtained by means of "Cellophane". The sections on brain and meninges, face and mouth, neck, thyreoid, mamma, and chest include records that will be of interest to those dealing specially with these parts of the body. This statement also applies to the sections on pulmonary tuberculosis and on heart and pericardium. There are several sections devoted to different aspects of abdominal surgery; they are full of interest and are well illustrated. First of all comes an opening section on the general aspects of abdominal surgery, and the following are dealt with in turn: the peritoneum, œsophagus, stomach and duodenum, small intestine, vermiform appendix, large intestine, hernia, liver, gall-bladder and bile ducts, pancreas and spleen. With so much of interest it is impossible in the space available to refer to any of these in detail. At the same time it must be pointed out that many operative procedures are described and well illustrated. Among these may be mentioned "aseptic" gastrectomy, total gastrectomy by the transthoracic approach, resection and anastomosis of the small intestine, and operations for removal of cancer of the colon. Sections on the spine and spinal cord and on the upper and lower extremities bring this volume to a close.

[1] "The 1944 Year Book of General Surgery", edited by Evarts A. Graham, A.B., M.D.; 1944. Chicago: The Year Book Publishers, Incorporated. 7" × 4½", pp. 736, with many illustrations. Price: $3.00, post paid; in Australia, 23s. 6d.

The Medical Journal of Australia

SATURDAY, MAY 12, 1945.

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INTERNATIONAL HEALTH IN THE FUTURE.

Now that the war in Europe is nearing its end and substantial progress is being made in the war against Japan, the minds of most people are turning to the winning of the peace. That this will be a most formidable task none can doubt, and it is unquestionable that unless the peace is "won" all the misery, death and destruction of the years of war will have been in vain. Many authors have dealt with this subject, and we may take it that most of their writings have been influenced by what is known as the Atlantic Charter and the four freedoms. In fact we may be quite certain that any plan for the future which disregards the spirit of the Atlantic Charter will receive scant consideration from the nations whose people will before long try to devise a plan of peace and are even now preparing for it. We recall the views of Sorokin in his book "The Crisis of Our Age" that the present world crisis represents the disintegration of a stage of world culture[1] and that the establishment of a new culture is dependent on the deliberate choice by society of a new form and a forsaking of the old. Somewhat the same idea lies behind Dr. Frank R. Kerr's "Days after Tomorrow", in which he pictures the world in the year A.D. 2000.[2] This is a world in which dwells righteousness, and it has been brought about by "an act of faith on the part of the nations" and then by a system of education. Such views as these envisage a fundamental change in man, a spiritual development, an altered sense of values; and a change of this kind is necessary in varying degree for almost any plan that may be evolved for the future. In support of this statement the views of almost any recent writer on the subject may be quoted. If we grant that the occurrence of this change in man's outlook is possible (to deny the possibility would be to seal the fate of humanity), we need not hesitate to consider the creation of machinery to carry into effect a carefully formulated plan.

[1] THE MEDICAL JOURNAL OF AUSTRALIA, November 7, 1942, page 423.

[2] "Days after Tomorrow: A Voice from 2000 A.D.", by Frank R. Kerr, D.S.O., M.D.; 1944. Melbourne: Robertson and Mullens. 7" × 5"; pp. 85. Price: 2s. 6d.

In virtue of their training, medical practitioners, considering the future of world affairs, will pay most attention to health and to every human activity bearing on it. But the world has shrunk, distances have been made negligible; all nations live as never before almost in one another's pockets and no one nation can claim to be self-sufficient and capable of living to itself. World economy of the future will have to deal, not with separate nations as such, but with the human race through its several units, the nations. To this end international law will be required, and the law will need to be administered by an international authority. Any inquiry, therefore, on the international control of health, or, if the term is preferred, the international prevention of disease, should be prefaced by reference to international law. It will probably be stated at once that international law has been in existence for some years, that its provisions, though held to be binding by some belligerents, have been flouted by others when it suited their convenience, and that for this reason peace conferences, such institutions as the Permanent Court of International Justice, and even the League of Nations itself were so much waste of time and need never have been initiated. If a law is disobeyed, if a court that administers the law is set at nought, it does not necessarily follow that the law is bad or that the court is worthless. In international matters disobedience to the law may have dire and far-reaching consequences, and examples may easily be recalled. Instead of trying to show how far humanity has benefited from laws relating to the conduct or nations—and that it has benefited is indisputable—it would be better to inquire whether mistakes of the past cannot be avoided in the future, imperfections made good and failure changed to success. This is clearly a matter for lawyers, and in the circumstances attention should be drawn to an address on the international law of the future by Manley O. Hudson, Judge of the Permanent Court of International Justice.[1] The address was delivered at the annual meeting of the American Bar Association last September. Hudson holds that if escape is to be found from recurring world wars, we cannot content ourselves with the reestablishment of international law as it existed in the past. The quest for a viable legal order in the world of States leads inevitably, he insists, into the central problem of organizing the community of States within which the international law of the future is to find its application. Hudson goes on to state—and his remarks will apply to countries other than his own—that if present national unity can be preserved, if it does not fall victim to divisions between parties, we can entertain high hopes that substantial progress in international organization can be made in our time. From the experience of twenty-five years it should be clear that "no one nation may be able to get all it wants in international negotiations, even if its people are unanimous in the desire". There will be no general international organization unless the nations are willing to take part in it in a measure commensurate with their power and prestige. When this decision is made a host of difficulties will vanish overnight. "We shall not arrive at a perfect solution, but we may console ourselves that what we do will not rest immutable through all the

[1] *International Conciliation*, Number 406, December, 1944, page 757. New York: Carnegie Endowment for International Peace.

ages and that men as inspired as we, as possessed of wisdom and virtue, will succeed us on the stage of world affairs." Hudson names three lines on which the international law of the future may be developed: (*a*) The proscription of the use of force for the service of national ambitions; (*b*) the improvement of pacific means for the settlement of international disputes; (*c*) the extension of existing law by a process of international legislation. He makes an interesting distinction between disputes that can be resolved by the interpretation and application of existing laws and treaties, and those which present "frontal challenges" to the prevailing laws and treaties. If progress is to be made in dealing with the latter, the task may have to be entrusted to men "who do not operate within the confines of the judicial process" — in other words, to politicians, whose business it is "to appraise and to canalize currents of opinion, and who by their authority at the moment are invested with a freedom to strike out along paths not blazed by the law and treaties in force". This means that judicial agencies should not be imperilled by being burdened with political functions. To the person interested in the subject but not versed in law all this does not sound very different from the old state of affairs. It may be that an extension of international law and the improvement of facilities to amend it when occasion arises will make a difference. Be that as it may, the crux of the situation must surely lie in a condition which will receive ready assent and is expressed by Hudson in the following words: "We cannot hope for much progress unless we are prepared to make some departures, to subordinate some preoccupations, and to cultivate some new loyalties. And perhaps one generation can but lay the foundations upon which a later generation may build."

Enactment of legislation is futile unless some authority comes into being which will administer the law and police its observance. After the war of 1914-1918 the League of Nations was established in the hope that the peace of the world would be preserved through its activities. That it was not completely successful is only too clear to the whole world today. It was not, however, a complete failure, but its measure of success cannot be estimated in this place. It must suffice to remark in passing that some of its most successful work was carried out in the matter of health. The forging of an instrument to meet the needs of the nations after the present conflict has been discussed by Wayne D. Williams,[1] who is a lieutenant in the office of the Judge Advocate General of the United States Army. His essay was awarded a prize in a contest conducted by the American Bar Association in 1944. At the outset Williams names one illusion that must be dispelled. This is the illusion that power and authority are divisible, that the occasion for the use of force may be determined by an international instrumentality, but the means of force left to national control. What he proposes is that the United Nations, acting in that name and by written constitution, should establish "a political instrumentality following the federal form, with delegated legislative authority and supremacy in the prescribed field". We need not follow Williams in his detailed proposals for membership of nations to this body or for the powers that it should hold. The point of importance is that the great powers would surrender military supremacy and the right to judge their own causes. "Wisdom dictates that they substitute the relatively slight burdens of a government, in which they will have a large measure of control, for the enormous burdens of major wars." What form any concerted action of the United Nations will take in the establishment of a central authority is not a subject for this discussion. At the present time the eyes of the world are on the San Francisco conference and we may expect definite proposals to emerge from it. On the wisdom displayed will depend not only the peace of the world, but also the well-being of the nations in different spheres of activity.

At this point we can return to the subject of our present discussion, the international prevention of disease and preservation of health. At the present, with the overture to UNRRA ringing in our ears, we are wondering what will happen when the curtain rises. This is only one aspect of international endeavour in the pursuit of health, but it is the most urgent problem at the moment. After this we recall the work of the Health Organization of the League of Nations, the labours of the International Health Commission of the Rockefeller Foundation, and of the first organization in the field, the *Office International d'Hygiène Publique*. Another body which should probably be mentioned in this select company is the League of Red Cross Societies. In the "new order" of the post-war period, when the United Nations have cemented their union by the establishment of an organization to bring their plans for humanity to fruition, there will be room for the functioning of the bodies named or of similarly devised bodies, and their functioning will be effective as the central organization is well founded and virile. A concluding reference may be made to the Hermann M. Biggs Memorial Lecture on international health delivered in April, 1944, before the New York Academy of Medicine by Wilbur A. Sawyer, Director of the International Health Division of the Rockefeller Foundation.[1] This author reminds us that the oldest and most generally accepted international health function is the regulation of quarantine. Of the organizations that have been named, the *Office International d'Hygiène Publique* was authorized at a convention in Rome in 1907 and soon afterwards occupied headquarters at Paris. It has been concerned chiefly with the prevention of the spread of the major communicable diseases. After the war of 1914-1918, when it was clear that an international agency covering a wide range was needed, the Health Organization of the League of Nations came into being at Geneva. Its operations have covered many subjects and have extended into many countries; a casual survey of its *Bulletin* will bear witness to this statement. It set up commissions to deal *inter alia* with malaria, with biological standards, with nutrition in relation to health, agriculture and economic policy, with prostitution. By no means the least important of its activities was the collection and distribution of current health information. The *Epidemiological Reports* issued quarterly were invaluable, and of particular interest to Australia were the reports that used to be broadcast each week from the Far Eastern Bureau. Sawyer states that attempts to merge the *Office International d'Hygiène Publique* and the Health Organiza-

[1] "What Instrumentality for the Administration of International Justice will most Effectively Promote the Establishment and Maintenance of International Law and Order?", *International Conciliation*, Number 406, December, 1944, page 774.

[1] *Bulletin of the New York Academy of Medicine*, July, 1944.

tion of the League of Nations were abortive, and he points out that the two bodies functioned separately but with a system of liaison which lessened the disadvantages. Both organizations are almost at a standstill because of the war, and Sawyer suggests that when general plans for health organization are again formulated it will be an opportune time to consider just how the world agency had best be set up and with what range of activity. This will presumably be a matter for whatever central organization is set up by the United Nations. The part taken by the International Health Commission, now styled the International Health Division, of the Rockefeller Foundation will not be described for lack of space. In any case it is a non-official and privately endowed agency, and, being controlled and directed with wisdom, it is probably on this account the stronger and more effective. It will doubtless continue its health-bringing work in any place where it is needed. For the official organizations that will function after this war is over, two of the principles stated by Sawyer may be mentioned: They should "help and advise the technical health officials of the several nations and facilitate cooperation among them, but without assuming to be a superimposed agency directing their work". Again: "The first aim should be to lead in searching out and defining important health needs, anticipating dangerous situations, and devising more effective methods than those we now have for protecting and improving health."

Current Comment.

KEROSENE POISONING.

THOUGH kerosene poisoning does not occur so frequently nowadays as it did a few decades ago, it is a condition of considerable interest. The effects of drinking kerosene vary from mild discomfort to death, generally preceded by pneumonic changes in the lungs. Children are most usually affected. Kerosene is distilled from petroleum and has a boiling point of 150° to 300° F. Its volatility is relatively low and differs according to the composition of the crude oil from which it is distilled. J. P. Price, in discussing the variability of the clinical picture,[1] referred to a statement by Sollmann that the toxicity of the ingested kerosene had to be taken into account, for the toxicity varied directly in proportion to its content of volatile products. Price also contended that a factor which determined the prognosis was the amount of kerosene that was aspirated during the act of drinking. He held that the involvement of the respiratory tract in children was brought about by aspiration of the liquid and by vaporization which followed as it was warmed by the heat of the body. He stated that although the boiling point of kerosene was high, the lower hydrocarbons which were present in all but the purest kerosenes, probably vaporized at body temperature and produced damage. This view has been held by other observers. Thus J. A. Nunn and F. M. Martin, in a report on 65 cases of kerosene poisoning occurring among children,[2] state that the prognosis is in direct ratio to the amount of hydrocarbon that enters the lungs. The patients in their series who aspirated, as well as ingested, kerosene presented a graver clinical picture than those who did not, owing to the rapid development of pneumonitis. They also refer to work by Waring, who was unable to find methæmoglobin in the blood in cases of kerosene poisoning. Waring, they state, showed by his experiments on dogs that as much as 100 cubic centimetres of kerosene administered by stomach tube produced only slight temporary ill effects, while "as small a quantity" as ten cubic centimetres injected into the trachea resulted in death in from six to eight hours. Nunn and Martin state that the pneumonitis is caused by the irritating properties of kerosene and that the evidence of involvement of the central nervous system (cyanosis, rapid and feeble respiration, rapid and weak pulse, restlessness, coma and convulsions) is due to the rapid and overwhelming absorption of the volatile fractions by the pulmonary circulation, this absorption being facilitated by the thin permeable alveolar wall.

A study on kerosene intoxication has recently been published by W. B. Deichmann, K. V. Kitzmiller, S. Witherup and R. Johansmann.[1] Their communication is based on the history of a fatal case of kerosene poisoning and they follow it with an account of some experimental observations. The history is that of a child, aged one year, who drank a mouthful of kerosene from a bottle found on the floor of his home. The stomach was washed out with baking powder solutions and the patient was admitted to hospital. The child was moribund and cyanotic. The mucous membrane of the nose was congested, the throat was intensely reddened and an odour of kerosene was detected in the breath. Respiration was irregular and gasping. Suction was applied to the throat and a moderate amount of mucus was removed. Vomiting occurred and the vomitus, which was small in amount, consisted of thick mucus with a strong odour of kerosene. The child died eight hours after admission to hospital and nine hours after drinking the kerosene. At autopsy the lungs were large and heavy and the pleural surfaces were dark reddish blue, but were spotted along the anterior borders by a few small light pink areas and a few slightly raised emphysematous blebs. Sections of the lung revealed moderately wet, uniformly reddened, fairly firm and practically air-free tissue from which a frothy fluid was expressed. A strong odour of kerosene came from the pulmonary tissue. The stomach was distended with gas and contained a small amount of tan mucus which had an odour of kerosene. Microscopic examination of the lungs revealed œdema, hyperæmia, some capillary endothelial swelling, focal areas of acute interstitial inflammation, small hæmorrhages, and exudate consisting of inflammatory cells in the alveoli. In some areas the fibrin of the exudate appeared condensed in a thick red to reddish blue membrane which was plastered against the alveolar lining. Some of the smaller bronchi and bronchioles were partially filled with exudate, but presented no evidence of inflammation of the mucosa or supporting tissue. Some which had an intact mucosa were diffusely infiltrated by inflammatory cells; others showed necrosis of the epithelium with an intense inflammatory reaction. The epithelium of the trachea and large bronchi was denuded in areas, a bare basement membrane being left. Deichmann and his co-authors state that in this case the fatal outcome was caused by rapid absorption of the ingested kerosene from the gastro-intestinal tract and its passage by way of the blood stream to the organs and tissues of the body, notably the lungs. "Here, as a result of its two-fold action, vascular and parenchymal damage occurred followed by the development of hæmorrhagic stasis, œdema and diffuse lobular pneumonia". These observers think that though the probability of aspiration of kerosene in regurgitated gastric fluid cannot be denied in most cases of clinical poisoning, it makes little difference, except to add to the damage already present. The findings in their case suggest that the child aspirated some kerosene in the first instance. The history points to the same conclusion, for the child swallowed a "mouthful" of kerosene and "coughing started immediately" and the subsequent signs and symptoms were most acute. It is, however, no use speculating on this point. What Deichmann and his colleagues wish to demonstrate is the twofold nature of lung injury in kerosene poisoning. They describe experiments on animals in which kerosene was given by intraperitoneal injection as well as by stomach tube. The

[1] *The Journal of the American Medical Association*, Volume XCIX, 1932, page 214.
[2] *The Journal of the American Medical Association*, Volume CIII, 1934, page 472.

[1] *Annals of Internal Medicine*, November, 1944.

pathological changes in the lungs were of the same general character, regardless of the means of administration, and death of the animal followed. Deichmann and his colleagues do succeed in showing that lung injury may be caused in two ways; but more work is needed in this subject, especially with different kinds of kerosene of which the content of volatile products is known.

THE TREATMENT OF DUODENAL ULCER.

THE treatment of duodenal ulcer is a subject that will always interest a medical audience. There are several reasons for this. The condition is relatively common and in recent years its frequency appears to have been increasing; divergence of opinion sometimes exists, not so much whether medical or surgical treatment is to be preferred, but when medical treatment should be set on one side in favour of surgical measures; the importance of the psychological aspect of the subject has given medical practitioners of all types much food for thought. Those who specialize in internal medicine have always been insistent on the value of medical treatment, on the institution of adequate measures (though from time to time opinions have altered regarding adequacy), and on their maintenance for a reasonable length of time. Surgeons have modified their views during recent years and are not so insistent as they used to be on the performance of surgical operation. This is well exemplified by Devine in his book on the surgery of the alimentary tract.[1] He states that the treatment of both acute and subacute gastric and duodenal ulcer will always be medical, even if these ulcers bleed. Omitting his reference to gastric ulcer, we read that in chronic duodenal ulcer with which are associated no definite ulcer diathesis and no secondary fibrotic changes medical treatment gives every prospect of permanent cure. When chronic duodenal ulcer is associated with a chronic, perhaps causative, diathesis, although temporary cures may be obtained under medical treatment, a permanent cure cannot be expected—and this because medical treatment cannot permanently modify the inherent causative factors. Devine points out that, although in the case of duodenal ulcer associated with a diathesis, with penetration, or with secondary fibrotic changes, medical treatment does not offer much prospect of permanent cure, it should be remembered that surgical treatment is not so successful and satisfactory as it is in chronic gastric ulcer in similar circumstances. He enumerates the factors on which the question of the medical treatment of peptic ulcer depends: (*a*) the factors in its causation, (*b*) the type and situation of the ulcer, (*c*) its response to treatment, (*d*) the presence of secondary complicating conditions. Then he continues: "A time may, however, come when a peptic ulcer will not respond even to the most faithful medical treatment; when for economic reasons the patient can no longer continue with medical treatment; when, as a result of secondary stenotic changes, nutritional disturbances begin to take place; or when the fear of cancerous degeneration arises. In these circumstances the question of surgical treatment has to be considered." The words "to be considered" should be noted; "undertaken" is not used. These views are quite clear and straightforward and many will be in agreement with them. Their application, of course, may be more difficult. In these circumstances it will be useful to note some remarks made at a discussion on the treatment of duodenal ulcer by the Section of Surgery of the Royal Society of Medicine in November, 1944.[2]

Sir James Walton opened the discussion and said that surgeons and physicians agreed that the one indication for surgical interference was the failure of medical treatment. He thought that even the presence of stenosis or hæmorrhage or even of perforation was in a sense evidence that the condition had not been cured medically. Sir Harry Tidy pointed out that surgeons often appeared to be satisfied that medical treatment had failed when the treatment followed would not have satisfied a physician. Of what, then, should medical treatment consist? And should the decision whether it has failed be left to the surgeon? Horace Evans said that it was a good practice in all but the clearest cases to cooperate with a surgeon from the outset, whether surgery was immediately in question or not. He had definite ideas about what medical treatment should be. He held that complete bed rest for a minimum period of six weeks, followed by a further six weeks of quiet convalescence, was essential. Mental relaxation was just as important as physical relaxation. Important factors in the production of unsatisfactory results were the early disappearance of the pain and the presence of a host of economic and domestic difficulties. To aid in the production of satisfactory results he recommended treatment of duodenal ulcer patients in a special ward. The total exclusion of unsuitable foods, tobacco, "and perhaps even the surgeon" made the burden easier and recovery more rapid. This is, of course, not compatible with "cooperation with a surgeon" from the start. C. Jennings Marshall maintained that the primary treatment of duodenal ulcer was medical and that its essential was physical and mental rest. He insisted that it was important to distinguish between cure of symptoms and cure of the ulcer, which persisted long after disappearance of X-ray signs and occult blood in the fæces.

The points in the discussion that have been mentioned are of fundamental importance. Many clinicians would give to the insistence on mental rest pride of place in treatment, and there is a great deal to be said for this view. Medical treatment must be adequate, and it may be applied by any practitioner. The surgery of duodenal ulcer is for the expert, and Walton holds that in regard to it no man is entitled to say that one form of treatment is alone correct. All that he can say is that it gives the best results in his hands; others may find different methods more suitable. In the discussion Walton and others dealt in detail with different types of operation and the indications for their use. Surgeons who are interested will read an account of the views presented. One remark that should perhaps be made is that medical practitioners, whether they are physicians or surgeons, will, if they have the misfortune to suffer from duodenal ulcer, avoid surgical operation for as long as they possibly can.

[1] H. B. Devine: "The Surgery of the Alimentary Tract", 1940, page 414.

[2] *Proceedings of the Royal Society of Medicine*, December, 1944.

THE WATERHOUSE–FRIDERICHSEN SYNDROME.

IT is indeed a dramatic illness which can in the course of a few hours bring about striking disturbances of consciousness, a state of shock evidenced by pallor with cyanosis and falling blood pressure, a rapidly spreading purpuric eruption and as a rule a rapidly fatal termination within a day or two or even less. Those interested in medical history will recall the accounts of some of the worst epidemics of meningococcal infections, "spotted fever", as it was called, in which such cases occurred. Others with experience of the last war may point to the somewhat similar clinical picture in some of the fulminating pneumococcal infections in which autopsy revealed gross hæmorrhagic spoiling of the adrenal glands. Waterhouse in 1911 and Friderichsen in 1918 pointed out that this syndrome is a clinical entity associated with a bacteriæmia, usually due to a meningococcus. Though we may deplore the addition of yet another name to the overlong list of medical labels, we must admit that the Waterhouse-Friderichsen syndrome now connotes a definite clinical state. Major V. C. D'Agati and Major B. A. Marangoni have among a number of recent writers dealing with the same subject made some correlation of the clinical and pathological data obtained from cases of this syndrome.[1] In a station hospital they observed six cases, five fatal but one with recovery. The onset was dramatically sudden, as severe meningococcal blood infections so often are. The most striking features were the profound degree of shock and the hæmorrhagic eruption. The latter progressed rapidly from a petechial rash to a purpuric one, some of the areas being large and showing sloughing. Vomiting, diarrhœa and abdominal pain were

[1] *The New England Journal of Medicine*, January 4, 1945.

frequent complaints. Fever occurred in the early stages, but the temperature fell to normal or below after twenty-four hours or so. The pulse rate was consistently rapid. There were usually basal râles to be heard in the lungs and frank pulmonary œdema was the herald of coma and death. In every case anuria was an early feature, and even after the period of initial shock the renal output was extremely low. D'Agati and Marangoni report the results of biochemical studies on their patients. These are important, for the rapidly lethal nature of this syndrome has hitherto made such investigations for the most part impracticable. An elevation of the non-protein nitrogen level was present in every case, and though the figures were not of themselves high, it is interesting that the blood creatinin levels were greatly raised, even to 9·0 milligrammes *per centum* in one case. The sodium-potassium balance was also deranged. Recently references were made in these pages to experimental Addison's disease in animals, and it was pointed out that with an increasing asthenia in the animal there were observed biochemical changes closely paralleled by these observations. This is not surprising, since hæmorrhagic lesions were found in the human adrenal glands after death, the shortest-lived patients showing the most extensive extravasations. Hepatic changes were also found, but in the case of the liver, the most extensive degrees of necrosis occurred in the cases in which the patients lived longer. It was only in these latter also that significant renal lesions were evident. There is thus abundant evidence that the more intense the adrenal spoiling, the more rapid the deterioration of the patient. D'Agati and Marangoni report the case of one patient who recovered, and state that only six such cases are reported in the literature. Their patient was an eighteen year old soldier in whom a diagnosis of meningococcæmia was made and confirmed by culture obtained from the blood and spinal fluid. The symptoms, though less acute than in other cases seen, pointed to adrenal involvement. Under intensive treatment with sulphadiazine and cortical adrenal hormone definite improvement was observed on the fourth day and the patient made a complete recovery. The authors stress the importance of the early shock and overwhelming toxæmia and point out that in cases in which this period is survived there is risk of hepatorenal failure.

Leonard D. Weinberg and Thomas H. McGavack also report a case of recovery from the Waterhouse-Friderichsen syndrome.[1] They carry back the history of the recognition of this condition as far as 1894, and point out that up to the present time no less than 157 cases had been reported in the literature. Their patient was fortunate to recover, as she was aged sixty-three years. In this case the onset was acute with collapse, cyanosis and petechial eruption, and meningococcæmia was proved by culture, but the chemical findings were less characteristic. Recovery was satisfactory following treatment with sulphadiazine and adrenal cortical hormone. The value of this hormonal therapy is becoming more firmly established, and it now rests on a satisfactory experimental and clinical basis. In cases of this syndrome an initial intravenous dose of 20 cubic centimetres of aqueous extract of adrenal cortex is advised by Weinberg and McGavack, followed by 15 milligrammes of desoxycorticosterone acetate given subcutaneously or intramuscularly, and an additional 10-milligrammes every eight hours until the systolic blood pressure remains over 100 millimetres of mercury. Smaller daily doses are advisable until convalescence is established. Vigorous dosage of a sulphonamide is essential and the usual measures to counter dehydration. Owing to the usual increase in meningococcal infections associated with war-time conditions, more opportunities have presented themselves for studying this dramatic and dangerous syndrome. Although its complete ætiology has not been worked out, it is likely that not only meningococcal but also pneumococcal, streptococcal and staphylococcal blood infections may initiate it, but in any case whatever the suspected nature of the infecting coccus, it is logical to proceed along the lines laid down by those whose therapeutic efforts have been successful.

[1] *The New England Journal of Medicine*, January 25, 1945.

ARTERIAL INJURIES.

ALTHOUGH much information is to be found in the recently issued memorandum by the Medical Research Council[1] on the subject of arterial injuries, one of the uppermost impressions gained on reading it is the incomplete state of our knowledge. What determines the extent and duration of arterial spasm following injury is apparently still unknown. There is strong evidence that Volkmann's contracture follows a purely arterial lesion and consists essentially in the replacement of ischæmic muscle by fibrous tissue, and we believe that today, most surgeons and pathologists accept this explanation. The true nature of "arterial stupeur" and of the so-called vasospastic reflexes to which Leriche has repeatedly drawn attention, remain as mysterious as ever. The clinical manifestations of complete division, thrombosis or spasm of a main artery, now more generally recognized, are described in detail in the memorandum. In this document, also, useful guidance is given to the approach to the patient suspected of having a vascular injury. We may quote the desirability of auscultation of main arteries near wounds, and the anatomical fact, not always recognized, that the peroneal artery may wholly or in part replace the posterior tibial with the consequence that instead of a pulse being present behind the ankle, it may be found anterior to the lateral malleolus. If in gunshot injuries producing fracture of the femur or wounding of the knee joint, the femoral or popliteal artery is damaged at the same time, gangrene of the leg almost invariably occurs. This coincides with experience in the last war as well as in civilian practice. The development of a collateral circulation is largely dependent on muscular branches of the main artery or its tributaries, so that where there has been much destruction of muscle as in some gunshot wounds, an adequate collateral circulation is unlikely to develop. Primary amputation may be indicated in such cases.

When we turn to the question of the treatment of arterial injuries we do not always find ourselves in complete agreement with the somewhat didactic and yet at times hesitant views expressed in the memorandum such as, "the main vein should probably also be tied when ligature of a main artery is indicated". We should have thought that the experiences of both the last and present wars, supported by the experimental work of Emile Holman,[2] had decided the value of this practice. Not all will agree with the statement that clinical evidence of a lateral wound in an artery is a definite contraindication to primary wound excision, and there is an air of unreality about the statement that a musculo-fascial barrier should be made around an open wound of an artery by suturing one or two layers of fascia or muscle over the wounded vessel. We cannot but wonder how many successful cases can be claimed from this procedure; certainly none that we have heard of, and we have inquired of surgeons dealing with arterial wounds in the forward fighting areas. Rather, would this procedure appear to us to be more likely to lead to thrombosis and gangrene than would wound excision, division of the damaged artery between ligatures, ligature of the vein, cooling and elevation of the limb with warmth to the body as a whole. An omission from the memorandum is the value of arterial ligature at an optimum site, as has been recently demonstrated by Emile Holman,[3] for example, of the femoral artery just below the prefunda rather than an inch or two lower in Hunter's canal, and the brachial just below and above the superior and inferior profunda branches respectively with excision of the intervening part of the artery. A valuable part of the Medical Research Council's report consists of the appendices giving the technique of heparin administration and sympathetic block.

[1] "Arterial Injuries: Early Diagnosis and Treatment", by the Vascular Injuries Subcommittee of the Medical Research Council War Wounds Committee (Medical Research Council War Memorandum, Number 13); 1944. London: His Majesty's Stationery Office. 9¾" × 6", pp. 21. Price: 4d. net.

[2] E. Holman: "War Injuries to Arteries and their Treatment". *Surgery, Gynecology and Obstetrics*, Volume LXXV, 1942, page 183.

[3] E. Holman: "Further Observations on Surgery of Large Arteries", *Surgery, Gynecology and Obstetrics*, Volume LXXVIII, 1944, page 275.

Abstracts from Medical Literature.

THERAPEUTICS.

Pneumococcic Meningitis.

A. J. WARING AND M. H. D. SMITH (*The Journal of the American Medical Association*, October 14, 1944) have described combined penicillin and sulphonamide therapy in pneumococcic meningitis. Before chemotherapy was introduced 99% of patients suffering from this condition died. Sulphonamides reduce this mortality to somewhere between 31% and 80%. The authors found that antipneumococcic serum was of doubtful value. Penicillin used alone produced seven cures among 21 patients treated by intrathecal and intramuscular injection. The latest method is to inject intravenously 0·05 gramme of the soluble sodium salt of sulphadiazine or sulphapyridine per kilogram of body weight freshly made up in 5% solution in distilled water. At the same time 0·1 gramme per kilogram is given by mouth or by stomach tube. From then on 0·2 gramme per kilogram is given each twenty-four hours. The above doses apply to infants. Adults receive 3·0 grammes intravenously and 2·0 to 4·0 grammes by mouth at once and later 1·0 gramme every four hours. Intramuscular and intrathecal administration of penicillin is started as soon as diagnosis is made: 2,500 to 5,000 Oxford units are given twice daily into the theca of infants for two or three days; thereafter one dose of 2,500 to 2,000 units is given daily. At the same time infants receive 1,500 to 2,500 units intramuscularly every three hours day and night until 12,000 to 20,000 units have been given. Older children and adults receive 10,000 to 20,000 units intrathecally every day and 5,000 to 10,000 units intramuscularly every three hours. Penicillin is given intrathecally in 5·0 cubic centimetres of sterile isotonic saline solution; 5·0 cubic centimetres of spinal fluid are first allowed to run off; the three upper lumbar interspaces are used in rotation for this procedure. Treatment is continued for at least six days after the last culture has been grown from spinal fluid; after this penicillin is withdrawn, but sulphonamide is continued for seven to fourteen days. Saline, glucose and plasma are given intravenously as necessary. For sedation paraldehyde given by stomach tube or by intramuscular injection is preferred to barbiturates, codeine and morphine. Of twelve patients, eleven recovered and one died.

Furunculosis.

R. COLEMAN AND W. SAKO (*The Journal of the American Medical Association*, October 14, 1945) describe their experiences in the treatment of multiple furunculosis with penicillin. Six infants, aged six months to three years, were treated for widespread boils. Local therapy and sulphadiazine were used for several days without effect prior to the use of penicillin. This preparation was then given, 5,000 to 10,000 units being injected intramuscularly every three hours until some 230,000 to 460,000 units had been given. Large fluctuant abscesses were opened and drained. In all cases there was a rapid response to treatment. The penicillin administration was maintained for an average of six days in three hourly doses. These results indicate a result far superior to any previous therapy for this condition.

Thiouracil.

E. LOZINSKI AND J. SIMINOVITCH (*The Canadian Medical Association Journal*, November, 1944) have recorded their experiences in the treatment of five patients with thiouracil, one of whom died. In rats thiouracil causes enlargement due to increased vascularity and hyperplasia of the thyreoid gland, with a fall in basal metabolism. In animals treated for several months glands sometimes exhibit irregularity of structure, but still present an orderly cellular arrangement. On cessation of treatment the glands rapidly return to normal and the basal rate also returns to normal. It is concluded that thiouracil acts by preventing the formation by the thyreoid of its specific hormone. Thiouracil is rapidly absorbed and rapidly excreted in the urine. In human subjects a fall in the number of white cells, skin rashes and hyperthermia have been reported and agranulocytosis has caused several deaths. In thyreotoxic patients thiouracil causes a fall in basal metabolism and a general improvement in health in ten to twenty-four days. However, if iodine has been given previously, three to five weeks are required for improvement. In general, thiouracil is effective in the treatment of patients who are not suited for surgery, but cessation of medication is as a rule followed by return of symptoms. The dosage recommended is 0·6 gramme in divided doses daily for two weeks, and then 0·4 or 0·3 gramme daily. The authors advise that patients should be under continued observation and that repeated blood examinations be made and basal metabolic rates estimated. Five patients were treated in the series reported by the authors. Good results were obtained in four cases, but the fifth patient, on a dose of 0·9 gramme daily, developed agranulocytosis after one month, with a chill fever, headache, weakness and sore throat. The number of white cells fell to 1,000 per cubic millimetre, and in spite of energetic treatment with "Pentnucleotide", crude liver extract and transfusions with fresh blood, the patient died sixteen days after the onset with a terminal pneumonia.

The Treatment of Meningococcal Meningitis with Sulphamerazine.

C. S. OLIVER AND D. G. ANDERSON (*The American Journal of the Medical Sciences*, November, 1944) have made a report on the treatment with sulphamerazine of 56 patients who suffered from meningococcal meningitis. Forty-one patients were adults and fifteen were children, twelve years of age or younger. The oldest patient was sixty-five years of age. All the patients presented the typical clinical picture of meningitis, and in every instance the diagnosis was confirmed by bacteriological methods of examination. The severity of the illness varied. Thirteen patients were regarded as mildly ill; in 24 cases the illness was of moderate severity; 19 patients were severely ill. The usual dosage of the drug was an initial dose of two grammes given by mouth, followed by a maintenance dose of one gramme every eight hours. In the case of children dosage was calculated on a basis of one gramme per day for every twenty pounds of body weight. Comatose patients and those who were otherwise too ill or uncooperative to take drugs by mouth were given the sodium salt of the drug intravenously in doses varying from two to five grammes. Treatment was continued until the patient had made a clinical recovery. The average duration of treatment was 8·4 days; the shortest period was six days and the longest fourteen. The average total dose of drug for adults was 24·8 grammes, with a range of 17·0 to 40·0 grammes. For children the average dose was 16·6 grammes, with a range of 8·5 to 30·5 grammes. Daily determinations of blood concentration of the drug were made. Fluids were given liberally; an effort was made to maintain a urinary output of at least 1,500 cubic centimetres a day. Alkali therapy was not used. One patient received serum because she failed to respond to sulphamerazine. No others received antiserum. In 35 cases clinical improvement became apparent within twenty-four to forty-eight hours of admission to hospital. Toxic reactions to the drug were manifested by 22 patients. There were no deaths. Among the toxic manifestations were: nausea and vomiting, three cases; fever, three cases; leucopenia, eight cases; granulopenia, two cases. One patient suffered from renal colic. The authors conclude that sulphamerazine is an effective agent in the treatment of meningococcal meningitis.

"Demerol."

C. G. HORI AND S. GOLD (*The Canadian Medical Association Journal*, December, 1944) discuss the use of "Demerol" in obstetrics and surgery. "Demerol" is a synthetic coal tar derivative with properties similar to those of morphine and atropine. Introduced in Germany as "Dolantin", it was called "Pethidine" in Britain. One hundred milligrammes given orally raised the pain threshold 50% for six hours. Fifty milligrammes given intramuscularly were twice as potent as 22 milligrammes of codeine, and 100 milligrammes given parenterally were equal to one-sixth of a grain of morphine as an analgesic. "Demerol" is said to relieve spasm of plain muscle in the ureter and bronchi. In this study it was given one and a half hours before operation, 100 milligrammes being administered with $^1/_{100}$ grain of scopolamine. It produced sedative effects in fifteen to twenty minutes; the effects lasted for one to two hours, without depressing respiration. In a series of fifty cases its effect on bladder function after operation was doubtful, and it did not appear to have any effect on intestinal tonicity or peristalsis. Of fifty obstetric cases, 100 milligrammes of "Demerol" given every four hours produced satisfactory sedation in thirty, and had no effect on the respiration of mother or child. Its effect was enhanced by the use of scopolamine.

NEUROLOGY AND PSYCHIATRY.

Alzheimer's Disease followed by Paralysis Agitans.

F. H. LEAVITT AND F. H. LEWEY (*The Psychiatric Quarterly*, January, 1945) report the case of a woman who had a transient psychosis at the age of twenty-six and a head injury at thirty-seven; after this she gradually developed a mental disability in which

she repeatedly attempted suicide. She recovered; but in her sixty-seventh year she developed symptoms of Alzheimer's disease with rapid memory failure and confusion. Later she developed intense rigidity accompanied by tremor which resulted in contractions of her limbs. She died in a demented condition at the age of eighty years. Necropsy showed marked atrophy of the frontal lobes; the basal ganglia had lost their configuration. There were numerous cortical plaques and fibrillary changes in the ganglion cells, and atrophy of the optic thalamus. The authors consider that *paralysis agitans* is an extremely rare sequel to Alzheimer's disease.

Psychosomatic Correlations in Migraine.

LEWIS R. WOLBERG (*The Psychiatric Quarterly*, January, 1945) reports the case of a twenty-eight year old male with anxiety hysteria, and migrainous attacks which had occurred bi-monthly for sixteen years, being quite dissociated from his phobic disorder, and which came to a sudden halt. Analysis shows that both the migraine and the phobias were rooted in a situation of compulsive dependency, the patient being reared by a neurotic, hysterical mother and a paranoidal aunt. He never knew his father, and suspected that he had been adopted. His mother displayed a domineering over-protection. Marriage only increased his migraine. Finally psychoanalysis disclosed the character structure of the psychosomatic problems. The author concludes that in cases in which the migraine "burns itself out" with advancing years or cure appears to come spontaneously the character structure has altered itself so that hostility is either diminished or its outward expression enhanced.

Clinical and Electroencephalographic Studies: The Electroencephalogram in Psychoneurotics.

ONE hundred electroencephalograms of psychoneurotics were observed by Hans Strauss (*The Journal of Nervous and Mental Disease*, January, 1945) in an investigation of psychoneurotic patterns; and these were compared with 100 control cases. The records were taken with a three-channel Grass electroencephalograph. The method adopted in the investigation is fully described; and a discussion on the "alpha activity" is reported. The patients were studied at rest and during hyperventilation. It was demonstrated that patterns with a high amount and good continuity of alpha activity were rarer in psychoneurotics than in the control subjects. Good patterns were rare in those patients who suffered with chronic anxiety and were experiencing difficulties in adjustment. It was found, however, that a correlation between a certain type of psychoneurosis and a certain type of electroencephalogram was not valid for every single case.

The Disease-Entity Boredom ("Alysosis") and its Psychopathology.

EDMUND BERGLER (*The Psychiatric Quarterly*, January, 1945) considers that boredom is a neurotic disease, representing an unsuccessful defence mechanism of the unconscious ego against reproaches of the inner conscience. In his opinion it is always associated with the following three disturbances: (*a*) weak or shattering sublimations; (*b*) inner inhibition of voyeurism (the "Peeping Tom" characteristic, scopophilia); (*c*) defence against masochistic pleasure. In the writer's view boredom underlies the constant longing for "fun", which is an inner protection from the danger. Boredom may be a transitory, though repeated, phase in many neuroses. The prognosis is unfavourable in untreated cases, which in the author's opinion may result in suicide, since the disease is not self-limited but progressive. Cure, he claims, is possible by psychoanalysis.

Delinquency in Adolescent Girls.

THE drastic changes of social living thrust upon society by war are, according to Dale B. Harris (*Mental Hygiene*, October, 1944), partly responsible for the increase of delinquent behaviour in adolescent girls—an increase of over 100%, for instance, in sex delinquencies among minor girls. Though the blame is laid upon the war, war itself brings no new problems, only old problems in a new setting. The war is responsible for new groups, for the extension of night work; and young boys and girls not yet out of school find employment in newly formed groups. Within these groups there is a changing social control of behaviour. New contacts are formed outside the family circle. Geographical mobility, due to the demands of war work, tends to laxity in the social control. Overworked parents give less attention to the training of their growing children. Certain wartime jobs in which young girls may become absorbed carry many more moral hazards than others. Even the glamour of military uniform becomes a factor in the heightening of temptation, and not infrequently increases the intimacy of casual contacts.

Aftermath of Operational Fatigue in Combat Air Crews.

ACCORDING to observations of Milton L. Miller (*The American Journal of Psychiatry*, November, 1944), about 30% of airmen returned from overseas combat have symptoms of operational fatigue. This term designates an anxiety state in which the individual is still attempting to deal with reactions to combat. There are three main groups in which the causative factors are: (*a*) hardships, excessive combat experiences, and unusually harrowing events which a normal personality cannot tolerate; (*b*) a previously well-masked psychoneurosis which emerges because the former methods of dealing with anxiety prove inadequate under combat conditions; (*c*) depression because of emotional involvement with a person whose death causes prolonged guilt and mourning reactions. Observation of over 800 subjects showed a uniformity of symptoms. Psychosomatic symptoms, though not an outstanding feature, may occur as an aftermath of operational fatigue. Attitudes toward further flying, towards civilian life, and towards the family may be profoundly affected by operational fatigue.

Capgras's Syndrome: A Peculiar Illusionary Phenomenon, Considered with Special Reference to the Rorschach Findings.

KARL STERN AND DOROTHY MACNAUGHTON (*The Psychiatric Quarterly*, January, 1945) report the history of two patients displaying the Capgras syndrome—a schizophrenic woman and a manic-depressive man. In this syndrome the patient fails to recognize the identity of a familiar person, but believes him to be the double of that person. In the first case there was a family history of paranoid psychosis, and the patient's mother also suffered from the illusion of the "double". In the discussion of the psychological and genetic aspects of the case, certain elements in the development allow a psychoanalytical interpretation and this is well substantiated by the "minus original" responses in the Rorschach record. In the second case the man exhibited the illusion of the "double" during two phases of his manic-depressive psychosis.

The Use of Drugs in the Treatment of Traumatic War Neurosis.

DRUG therapy in the traumatic war neurosis is used, according to Robert G. Heath and Stephen H. Sherman (*The American Journal of Psychiatry*, November, 1944), to enable the patient to face his traumatic experience and to uncondition him to it. Three methods are advocated: (*a*) the use of sedative to secure rest; (*b*) intravenous use of barbiturates to promote mental catharsis, the recall of a suppressed episode being thereby assisted; (*c*) use of drugs acting directly on the autonomic nervous system. The writers claim that if the central nervous system is depressed by sedatives the fatigue state may be cured. Narcosynthesis not only reduces automatic overactivity by depressing the hypothalamus, but promotes mental catharsis and therefore hastens the unconditioning process. Drugs may go beyond the war experience by stirring up old neurotic conflicts which may merge with combat reaction and tend to induce chronicity. Ergotamine interrupts the physiological circle of battle reactions by neutralizing adrenaline. Desensitization of traumatic memories is thereby hastened.

Symptomatology and Management of Acute Grief.

ERICH LINDEMANN (*The American Journal of Psychiatry*, September, 1944) contends that: (i) Acute grief is a definite syndrome with psychological and somatic symptomatology. (ii) This syndrome may appear immediately after a crisis; it may be delayed; it may be exaggerated or apparently absent. (iii) The typical grief syndrome may be displaced by distorted pictures. (iv) These distortions may by appropriate treatment be transformed into normal grief reactions and resolved. His observations were made upon 101 patients. Symptoms were remarkably uniform: common to all were sensations of somatic distress occurring in waves, a feeling of tightness in the throat, choking and shortness of breath, an empty feeling in the abdomen, and lack of muscular strength. In addition to somatic distress there were: (*a*) guilt, (*b*) preoccupation with image of the deceased person, (*c*) hostile reactions, and (*d*) loss of patterns of conduct. Prognostic evaluation and management are discussed. A combination of benzedrine by day and "Sodium Amytal" by night is advocated during the acute stage. Simple psychotherapy is strongly advised.

British Medical Association News.

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioner has been released from full-time duty with His Majesty's Forces and has resumed practice as from the date mentioned:

Dr. Lorimer Dods, 135, Macquarie Street, Sydney (April 23, 1945).

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on September 13, 1944, at the Children's Hospital, Carlton, Melbourne, the Acting President, DR. H. DOUGLAS STEPHENS, in the chair.

Bronchiectasis.

DR. J. G. WHITAKER showed a male child, aged five years and three months, in whom lobectomy had been followed by an unfortunate result. Dr. Whitaker said that for this reason the child was being shown, and he trusted that his audience would be tolerant enough not to judge all lobectomies on this as a standard. He wished to demonstrate how things might go astray. The child had been admitted to hospital on April 15, 1941, at the age of one year and four months, with a history of wheezing which had persisted since whooping cough and bronchopneumonia six months previously. Examination at this time revealed diminished air entry and raised pitch of breath sounds at the base of the right lung. Inspiratory and expiratory rhonchi were audible over the whole of the right lung. The left lung was normal. X-ray examination of the chest one week earlier had revealed enlarged right hilar glands and infiltration in the lower part of the right lung. The Mantoux test failed to produce a reaction with tuberculin diluted to 1 in 1,000 and again when diluted 1 in 100. Subsequent to this examination the child showed steady improvement, both physically and in the clinical signs. X-ray examination of the chest on May 10, 1941, had revealed diminution in size of the hilar glands and of the area of infiltration in the right lung.

On August 12, 1941, a bronchogram was prepared. This revealed bronchiectasis in the collapsed medial lobule of the lower lobe of the right lung. One week later bronchoscopy was carried out. Some narrowing of the bronchus to the lower lobe of the right lung was visualized. This bronchus was observed to contain a little mucopurulent secretion, but there was no evidence of stricture or foreign body. On September 10, 1941, the child was presented at a meeting of the society; lobectomy was considered advisable.

On February 20, 1942, right lower lobectomy was carried out after the induction of a preliminary pneumothorax. The few adhesions between the collapsed lobe and the diaphragm and middle lobe were easily separated. The child's condition was good after the operation and recovery was uneventful. An X-ray film taken on March 6, 1942, showed satisfactory aeration of the right side of the chest; no fluid could be demonstrated and the remaining portions of the right lung appeared to be normal. In April, 1942, the boy had a severe attack of bronchitis associated with a great deal of wheezing. Sensitivity skin tests were carried out, but the response was negative to all the common proteins. There seemed to be some response to ephedrobarbitone tablets. However, the child was subject to frequent colds with accompanying wheezing. In July, 1942, the tonsils were removed and the adenoids curetted. Since then he had had a persistent cough and suffered from frequent wheezing attacks, which, however, did not distress him. Between attacks he was energetic, but had lost some weight.

An X-ray examination on September 26, 1944, revealed almost complete collapse of the right lung. The left lung was normal. A bronchogram on September 31 showed extensive bronchiectasis throughout the collapsed right lung. Dr. Whitaker said that the question arose whether the operation was responsible for the bronchiectasis in the upper lobe, or whether universal bronchiectasis existed throughout the right lung prior to operation. The latter supposition seemed more likely, although Dr. Colin Macdonald had reported that the first bronchogram showed a normal bronchial tree in the right upper lung field. Dr. Whitaker said that he was anxious to hear from the members of the society how this result was brought about. At the operation the diseased portion of the lung was hepatized in appearance. Another question was whether this lobe was collapsed at birth and bronchiectasis had occurred secondarily. Dr. Whitaker concluded by asking the members not to refrain from submitting suitable patients for lobectomy because of this unusual complication.

DR. HENRY SINN said that the air of pessimism that surrounded the child did not appear to him to be entirely justified. The problem now was one of massive collapse of the lung, or rather of the remaining portion of the right lung. Dilatation of the bronchi inside the collapsed lung was a compensatory phenomenon. If collapse of a lung or lobe of a lung occurred, certain phenomena followed, which could be demonstrated radiologically, to compensate for the vacuum caused by the collapse—namely, over-expansion or emphysema of the remaining lung, elevation of the diaphragm on the same side and dilatation of the bronchi inside the collapsed lobe. The last-mentioned phenomenon had been found in true atelectasis occurring in newborn babies. It had to be remembered that spontaneous recovery was possible from the collapse, and the bronchiectasis cleared at the same time. However, if infection became superimposed on the dilated bronchi, the chances of spontaneous reexpansion were lessened and the bronchiectatic process became irreversible. Dr. Sinn said that he did not propose to discuss the causes of pulmonary collapse, but the impaction of a tenacious plug of mucus was a well-recognized factor. This frequently occurred as a sequel to bronchopneumonia, and a perusal of this child's past history suggested that this factor might have played a prominent role in the initial collapse as well as in the massive collapse present at the time of the meeting. Dr. Sinn said that he was not in a position to discuss the advisability or otherwise of the first operation, but he trusted that Dr. Whitaker did not propose to carry out pneumonectomy of the remainder of the right lung. Dr. Sinn suggested that bronchoscopy be carried out and that the contents of the right bronchial tree should be aspirated, and also that "Carbogen" should be administered under pressure. In conclusion, Dr. Sinn said that in his opinion the prognosis was not so bad as it appeared at first sight, and that physicians need have no fear on this account of submitting suitable patients suffering from bronchiectasis to the care of Dr. Whitaker.

DR. HOWARD WILLIAMS said that his association with the case had begun when the child was two years old. The illness began with pertussis and bronchopneumonia at the age of eighteen months. After this the child had a persistent loose cough, and respiration was wheezing in type. Subsequent investigation revealed a collapsed basal lobe in the right lung. The child was kept under observation for five months. Râles and rhonchi were persistently audible over the affected area. It was decided that the lobe had been given a fair chance to expand, and the child was submitted to Dr. Whitaker for lobectomy. He made a good recovery from the operation, but during the following six months he suffered repeated respiratory infections, and the clinical response was poor. Dr. Williams said that he was struck by the pronounced deterioration in the clinical condition. He said that he found it difficult to believe that the child was not suffering from gross bronchiectasis, and he would be surprised if any degree of recovery occurred. He viewed the child's future with dismay.

DR. L. WAIT said that surgical treatment was indicated in the first instance. In the ætiology of bronchiectasis, infection played the major part. He made a plea for more team work in such cases. Bronchoscopy was a useful preliminary. He recalled a patient in whom a foreign body was discovered in the unaffected lung. Bad luck had dogged the child under discussion. He thought that the outlook was not good.

DR. J. W. GRIEVE supported the view taken by Dr. Williams. He said that Dr. Williams had pointed out a triangular shadow at the base of the left lung, suggesting pulmonary collapse. Dr. McColl was now looking after the child. He was of the opinion that a lot of damage had occurred to the remaining lung.

DR. ROBERT SOUTHBY supported Dr. Sinn's plea to persevere with the case from the medical aspect. He recalled a patient whom he had examined several years earlier, who was coughing up half a cupful of offensive pus each morning. She was sent to the country, and returned fairly well; she had since gone through pregnancy with impunity. Dr. Southby suggested that if the child under discussion was sent to Frankston, considerable improvement might follow.

DR. W. W. MCLAREN said that if there was a history of repeated infection of the upper part of the respiratory tract with spread down to the lung, and if signs were demonstrable at the bases of both lungs, the prognosis was not good. However, if such children were put to bed in the early stages of the disease, in many cases resolution occurred without surgical interference.

DR. H. DOUGLAS STEPHENS said that in view of the different expressions of opinion he trusted that the patient would be shown at a subsequent meeting of the society.

Dr. Whitaker, in reply, said that he could not believe that the patient would do well. Bronchoscopy had been carried out. He did not contemplate any further surgical procedure.

Diaphragmatic Hernia.

Dr. Whitaker's next patient was a male child, aged six years and six months, with a right-sided diaphragmatic hernia. The child had been born at term after a normal labour and had weighed seven and a half pounds. He had suffered from bronchopneumonia at the age of three and a half months, but had had no other serious illness. He had frequently vomited when a baby. During the past eight months he had had occasional attacks of nausea and vague pain in the lower part of the abdomen after meals. Pain was relieved by vomiting. The child was otherwise well. His appetite was good and he was not subject to colds. He was energetic and never short of breath. The bowel actions were regular. He did not seem to be gaining in weight. On examination, he was a healthy looking, intelligent child. The apex beat of the heart was situated in the fifth left intercostal space inside the nipple line. The heart sounds were regular and clear. Gross "pigeon chest" with prominence of the sternum was present. The percussion note was resonant over the anterior part of the chest; the percussion note was dull and the breath sounds were diminished over the base of the right lung posteriorly. Over other areas the breath sounds were vesicular in type. No adventitious sounds were audible. The *recti abdominis* muscles were prominent and the liver was palpable to the level of the umbilicus. X-ray examination revealed a right-sided diaphragmatic hernia and a hiatus in the right hemidiaphragm lay posteriorly; portion of the duodenum and the remainder of the small intestine, caecum and proximal part of the colon were herniated into the right hemithorax. The heart shadow was not displaced to the left. The presence of intestines in the chest had produced "pigeon" deformity.

Dr. Whitaker said that the condition was rare, in that it was right-sided, and the hernial sac contained most of the abdominal viscera. Harrington had one case in his series of diaphragmatic herniæ, Dunhill none and Poate one. Poate made a right upper abdominal approach. The small bowel and colon were replaced in the hernia because there was no room for them in the abdomen. Poate could find only eleven references in the literature. Dr. Whitaker said that he had contemplated paralysing the phrenic nerve. As the child was now healthy and well, he did not think operation was indicated.

DR. ROBERT SOUTHBY said that he was interested in the rarity of right-sided herniæ. He recalled a baby suffering from repeated attacks of what was called "acidosis"—abdominal pain and vomiting. Dr. Allen on one occasion, whilst palpating the abdomen, had heard a gurgle, and noticed that this was accompanied by relief of the pain. The child's mother had remarked that her son always got better after she heard such a sound. Dr. Allen on this evidence diagnosed an internal hernia. X-ray examination, however, gave negative results. The child subsequently died of bronchopneumonia, and the diaphragmatic hernia was demonstrated at autopsy. In the case under discussion, Dr. Southby thought it wise to be conservative.

DR. L. WAIT said that he, too, was interested in the rarity of the anomaly. He had sent a baby to the hospital with a diagnosis of diaphragmatic hernia. This was verified at post-mortem examination, when the hernia was discovered on the right side.

DR. ERIC PRICE recalled another patient who was subject to similar attacks of "shock". He had been brought into the hospital and seen as an emergency patient. He presented the picture of shock without evidence of hæmorrhage. Dr. Price said that he had spent six hours trying to give him a blood transfusion. At operation a volvulus was found. Possibly the attacks of pain and vomiting were attributable to volvulus complicating the hernia.

DR. H. DOUGLAS STEPHENS said that he had never seen a right-sided hernia of such dimensions as in Dr. Whitaker's patient. Paraœsophageal herniæ were more frequent. He had operated on five patients with left-sided diaphragmatic herniæ. No sac could be found; apparently the herniæ had simply burst through the diaphragm. Dr. Stephens had seen the stomach in a left-sided diaphragmatic hernia. In his cases no great difficulty had been experienced when the transthoracic approach was used. The patients had done well, except one; his hernia recurred and he died from volvulus. Dr. Stephens said that the most difficult time to make the diagnosis was soon after birth. In the case under discussion he would not operate. He thought that the diaphragm would be as thin as tissue paper, and operative treatment would not help. Dr. Charles Osborne had had a similar case, in which he had tried to effect a repair through an intrathoracic approach. However, the wound burst. He later tried the combined abdominal and intrathoracic approaches, after which the patient died.

Dr. Whitaker, in reply, thanked Dr. Stephens for his helpful remarks. He said that few patients were subjected to operation. Paraœsophageal herniæ could appear on the right or left side. In the case under discussion he proposed to do nothing.

Ectopia Vesicæ.

DR. WILFRED FORSTER presented two children suffering from *ectopia vesicæ*. The first was a male child, aged six years and ten months, who had first been admitted to hospital on August 24, 1944. The condition had been present since birth. At the present time his general health was good. Urine was continually dribbling away from him. The bowel action was regular, though rectal prolapse occurred occasionally.

On examination, he was seen to be an apprehensive, nervous child. The heart and lungs were normal. The abdomen was thin and lax. No mass was palpable. A large fleshy mass covered with mucous membrane was present in the suprapubic region; it was the size of a small plum, with ureters opening at the surface. The scrotum was partially developed, but no testicles were palpable. The dorsal surface of the penis was normal. The anterior surface was undeveloped and connected with the mucous membrane of the bladder opening to the surface. On September 1, 1943, a Coffee III operation was carried out on the left side. A left lower paramedian incision was made after a pack had been sewn over the open bladder area on the abdominal wall. The rectus sheath was opened, the rectus muscle was retracted and the peritoneum was opened. The bowel was packed off and the left ureter was identified as it crossed the pelvic brim. The peritoneum of the posterior abdominal wall was incised over the ureter, and the ureter was dissected out as far distally as possible, care being taken to preserve its blood supply. The ureter was then clamped and divided, both ends being tied off. The outer coats of the lower part of the sigmoid colon were divided until the mucosa bulged through for about one inch in length. The cut end of the ureter was embedded between the mucosa and the muscle coat of the lower part of the sigmoid, and a slough stitch was tied between the ureter and mucosa of the sigmoid, so that when the stitch sloughed an opening would be made between the ureter and sigmoid colon. The peritoneum was sutured over the bare area on the posterior abdominal wall where it was incised, and the abdominal wall was closed in layers with drainage. Post-operative treatment consisted of the administration of sulphanilamide tablets, one three times a day, and nitrohydrochloric acid, five minims every four hours. During convalescence the wound healed well. The general health remained good. The patient had control over the anal sphincter. On October 30, 1943, he had an elevated temperature, and was considered to have a urinary infection, and so was given potassium citrate and sulphanilamide. On November 5, 1943, an excretion pyelogram was made; both kidneys were seen to be functioning well in response to the dye test; the ureters were slightly dilated, but the calyces appeared normal. On November 10, 1943, a Coffee III transplantation of the right ureter was performed. A right lower paramedian incision was made and the peritoneum was opened with the patient in the Trendelenburg position. The pelvis was inspected and adhesions were found between the small bowel and colon. These were divided. The caecum was found adherent to the sigmoid colon, and was freed. The sigmoid colon was identified. The right ureter was traced from the pelvic brim round the lateral pelvic wall. The peritoneum over the ureter was incised and the ureter was dissected out, clamped, tied and divided distally. The serous and muscle coats of the sigmoid colon were divided longitudinally for a length of one and a half inches, and the divided end of the right ureter was embedded in the wall of the sigmoid between the mucosa and the muscle layer. A sloughing suture of silk was inserted between the lumen of the sigmoid and the lumen of the ureter and the muscle coat of the sigmoid was sutured over the ureter for a length

of one and a half inches. The wound was closed in layers, a drain being left in the pelvis. The child's post-operative condition was good. On November 14, 1943, he was passing urine rectally. On December 6 the blood urea level was 22 milligrammes per 100 cubic centimetres. On November 30 an excretion pyelogram was made; both ureteral transplants appeared to have been successful. On December 22 he was sent home, taking potassium citrate and five pints of fluid a day; he was receiving a normal diet.

Dr. Forster said that in all such patients hydronephrosis was present, but this existed prior to operation. He made a plea for early operation in these cases. Early operation saved the work of the mother and prevented the child from becoming introspective. The rectum became accustomed to collecting urine, and the child was now able to hold the urine for four or five hours. The remaining problem was how to deal with the base of the bladder, which was exposed in the lower part of the abdomen. Dr. Forster said that he wondered whether he should try to excise it and to bring the skin over it. He wondered also whether, if the mucous membrane was buried, a deep cyst might form. The administration of sulphanilamide as a pre-operative measure was found useful in preventing infection in such cases.

Dr. Forster's second patient was a male child, aged two years and four months, who had suffered from *ectopia vesicæ* and bilateral inguinal hernia since birth. On July 15, 1943, the left inguinal hernia became strangulated and a left herniotomy was performed. On September 10 the right inguinal hernia became strangulated and a right herniotomy was performed. On August 20, 1944, he was readmitted to hospital for operation on the *ectopia vesicæ*. His general health was good. He had had rectal prolapse at intervals during the preceding ten months.

On examination, the boy was healthy and well nourished. The heart and lungs were normal. The abdominal wall had a deficiency in the suprapubic position. Red mucosa was visible in the opening. The penis was held up against the pubic region. Both testes were present. Pre-operative treatment consisted of a residue diet, half a sulphanilamide tablet every four hours, and bowel washouts every day. Operation was performed on August 23. In the first stage one ureter was transplanted. A lower median incision was used; the left ureter was exposed on the surface of the posterior part of the peritoneum; the peritoneum on the posterior surface of the bladder was incised; the ureter was cleaned, divided and tied with silk and then dilated to twice the normal size. An incision was made over the peritoneum of the upper third of the rectum and deepened to the mucosa. The seromuscular flaps were dissected out and the distal half of the ureter was embedded in the submucosa by oversewing of the flaps. The peritoneum at the base of the bladder was sutured and the abdomen was closed in layers. A drain tube was placed to the base of the bladder and sewn in with silkworm gut sutures. After operation the patient was given one sulphadiazine tablet every four hours, and thirty grains of potassium citrate were administered every two hours until the urine was alkaline, then every four hours. During convalescence the patient was miserable for five days and his temperature was elevated. On August 30 the tube was removed and on September 4 all sutures were removed from the wound. The general condition was satisfactory. The wound was moist and not very clean. On September 7 an excretion pyelogram was made and this procedure was repeated on September 12.

Dr. Forster said that in this case difficulty had been experienced in making a pocket into the anterior rectal wall. There was a danger of perforating the rectum in such cases. When the abdomen was opened, it was seen that hydroureter existed on both sides. The large ureter made it difficult to make a pocket between the muscle coat and mucosa. This was overcome by invaginating the serous coat.

DR. J. C. WHITAKER said that he had tried the Coffee III operation without success; death had occurred in all cases. When the ureter was exposed, it became denuded of its blood supply and underwent necrosis. It had also to be noticed that the abdominal wall would not tolerate urine for too long. Dr. Whitaker complimented Dr. Forster on his success.

DR. H. DOUGLAS STEPHENS also congratulated Dr. Forster. He said that the American surgeons also discarded the Coffee III operation, and he had never performed it. He had transplanted a rosette of one ureter with a catheter into the bowel on each side. These patients became introspective and changed mentally on reaching adult years.

Dr. Forster, in reply, said that in each case the child had a stormy convalesecence. He thanked Dr. Whitaker and Dr. Stephens for their remarks.

Sturge's Disease.

DR. L. WAIT showed a female child, aged six years, suffering from Sturge's disease. Ten weeks earlier she had begun to have "turns" in which she went limp, dropped whatever she was holding and stared in front of her for a few moments, seeming unaware of her surroundings. Sometimes she would answer questions. Immediately after the attack she would continue with whatever she had been doing before. At first she had had two or three attacks per day, but at the time of the meeting they were more frequent, and she might have ten or twelve per day. In the past two weeks her legs had given way and she had fallen during the attack. She became pale, but never twitched or had any stiffness or rigidity of the limbs. She had occasionally passed urine during these attacks, but had never bitten her tongue or lost control of her bowels. She had never vomited or complained of headache. No strabismus, no double vision and no disorder or sensation was present. She was mentally an alert child, she slept well, the bowels were open daily and her appetite was good. There was nothing relevant in her past history. Her maternal grandmother had suffered from "fits"; but was still alive and well. Her paternal great-grandmother also suffered from "fits".

On examination, a hæmangioma was present over the right supraorbital region. The heart, lungs, abdomen and central nervous system were clinically normal. The *fundi oculorum* were normal. The child suffered no attacks whilst in hospital. On September 9, 1944, an encephalogram was prepared by Dr. Graeme Robertson. X-ray examination of the skull revealed intracranial calcification in the right parieto-occipital region, suggesting calcification in the cerebral cortex such as occurred in Sturge's disease. The cerebro-spinal fluid contained no cells; the chloride content was 752 milligrammes per 100 cubic centimetres, and the protein content 20 milligrammes per 100 cubic centimetres.

Dr. Wait said that the child was shown because of the rarity of the disease. Up to 1939 only 145 cases had been reported. The condition was congenital and perhaps hereditary. The main abnormalities seen were: (i) a cavernous nævus of a port-wine colour in the distribution of one or more branches of the trigeminal nerve; the overlying skin might hypertrophy; (ii) vascular changes in the eye on the same side, with glaucoma and exophthalmos in one-third of the cases; (iii) changes in the *pia mater*, varying from slight telangiectasis to a racemose venous angioma; (iv) pronounced cerebral changes—namely, hypoplasia, atrophy and calcification confined to one side of the cerebrum. The calcification was partly perivascular and partly a deposit of free calcium granules in the brain. The symptoms of cerebral affections arose early in life, often before the age of ten years, and consisted of either focal or generalized epileptiform seizures, hemiplegia, hemiatrophy or some degree of amentia. The commonest site of calcification was the occipital cortex. The immediate prognosis was good, but in the more severe forms mental degeneration had to be expected subsequently. Operations attempted included removal of diseased cerebral areas, ligation of the common carotid artery and decompression. All these operations had given poor results. X-ray or radium therapy had been of value.

DR. ROBERT SOUTHBY said that he was interested in the similarity between Dr. Wait's patient and the child he had presented at a meeting of the society as an example of the Brushfield-Wyatt syndrome two or three meetings earlier. There seemed no doubt now that this was an error, and that the condition really fell into the category described under the term "Sturge's disease" by Dr. Wait. Calcification might be expected to occur as this child grew older. Dr. Southby said that in his case, the baby had been in good health until the age of five months, when he had a convulsive seizure; Dr. Southby noticed a similar onset in Dr. Wait's case. Dr. Southby said that it was well to remember that the first convulsive seizure might be an early manifestation of some serious disorder; it showed the importance of a thorough routine investigation of all these patients, even though one was often disheartened by negative findings.

Medical Practice.

REGULATIONS DEALING WITH DRUGS.

THE two following communications received by the Victorian Branch of the British Medical Association from tthe Collector of Customs are published for the information of readers.

COMMONWEALTH OF AUSTRALIA.

Customs and Excise Office,
Flinders Street,
Melbourne, C.1.

Dangerous Drugs: Importation and Exportation.

Dear Sir,

With reference to control of dangerous drugs, you are advised that information has been received from the Comptroller-General of Customs that the following drug has been added to the list of drugs covered by Item 4A (paragraph (s)) of the Third Schedule of the Customs (Prohibited Imports) Regulations, and Item 6 (e) of the Fourth Schedule of the Customs (Prohibited Exports) Regulations:

Pethidine Hydrochloride.

Pethidine Hydrochloride is a synthetic drug which, if improperly used, is likely to be productive of harmful effects similar to morphine and the Minister has decided that the drug is to be dealt with in a manner similar to that relating to the latter narcotic.

In America, the trade name of the drug is "Demerol", and in that country is designated by the chemically descriptive term "Isonipecaine".

Pethidine is also known in Europe and South America as "Dolantin".

It is requested, therefore, that appropriate action be taken relating to keeping of records, etc., in respect of Pethidine Hydrochloride in any form which may be held in stock and that control of the drug be exercised in a manner similar to that appertaining to morphine.

Yours faithfully,
F. TERRY,
Collector of Customs, Victoria.

AMENDMENTS OF THE CUSTOMS (PROHIBITED IMPORTS) REGULATIONS.

1. The First Schedule to the Customs (Prohibited Imports) Regulations is amended by omitting item 15A.

2. The Second Schedule to the Customs (Prohibited Imports) Regulations is amended—

(*a*) by omitting the word "bran" in item 3 and inserting in its stead the words "chaff or bran"; and

(*b*) by inserting after item 9 the following item: "9A. Foods, drinks and medicines, for use by man, and preparations (including essences and extracts) used in the manufacture or preparation of foods and drinks for use by man, which contain any of the glycols or their derivatives."

3. The Third Schedule to the Customs (Prohibited Imports) Regulations is amended by omitting paragraph (n) of item 4A and inserting in its stead the following paragraph:

"(n) galenical preparations (extract and tincture) of Indian hemp, and preparations (excepting such preparations as are capable only of external use) made from extract or tincture of Indian hemp;".

Correspondence.

RUBELLA AND CONGENITAL DEFECTS.

SIR: With regard to the letter in your issue of April 21, 1945, from Dr. Charles Swan, I wish to assure Dr. Swan, Dr. Tostevin and their colleagues that there has never been any question about the complete independence of Dr. Tostevin's discovery, as pertaining to South Australia, of the association between congenital deaf-mutism and maternal rubella. On the contrary it has always been regarded here that the observation of this association made in Sydney in 1942-1943 by several consultants and similar observations made in Adelaide were entirely independent of each other. I have felt that this complete independence of similar observations in the two States has added to their importance and clinical worth.

Moreover, this association was first described in THE MEDICAL JOURNAL OF AUSTRALIA, September 11, 1943, page 201, in the excellent contribution by Dr. Swan *et alii* to which I have already paid tribute elsewhere (*Transactions of the Ophthalmological Society of Australia (British Medical Association)*, Volume IV, 1944; in the press).

Whether Dr. Swan was justified in forming the impression he did from my paper is, I think, a matter of opinion. That he did gain such an impression is for me a matter of the greatest concern and regret. I am deeply upset that any words of mine should have been construed as to appear to detract in the slightest degree from the excellent work performed by Dr. Swan and his colleagues.

In my paper no claim was made for the discovery of the association between rubella in pregnancy and congenital deaf-mutism. As far as this State (New South Wales) is concerned and within my knowledge, it is my humble opinion that any credit due for such discovery must go to the three mothers who, as mentioned in my paper, separately and acting on their own initiative contacted me in December, 1941, and so afforded Dr. Blashki and myself the opportunity of observing the association.

Yours, etc.,
N. M. GREGG.

193, Macquarie Street,
Sydney,
April 30, 1945.

SIR: What causes (other than German measles) are responsible for congenital deaf-mutism? Is it possible that repeated large doses of quinine taken in the early stages of pregnancy in an effort to produce a miscarriage can also be responsible?

Yours, etc.,
April 30, 1945. MEDICUS.

SIR: Since 1941 reports by Gregg, Carruthers and Swan have appeared in THE MEDICAL JOURNAL OF AUSTRALIA concerning congenital defects occurring in children born of women who had suffered from rubella or rubella-like infection early in pregnancy.

With regard to congenital deaf-mutism, a recent article by Murray and Wilson draws attention to the association of congenital deafness or mutism with districts where low iodine content of water supply gives rise to endemic goitre and cretinism. Similarly other workers have reported on this association. Three districts of Oxfordshire with a population of 36,000 odd and a water supply low in iodine (1·4γ to 3·0γ per litre) produced 28 deaf mutes on investigation. The suggestion is made by these workers "that a biological factor such as a low amount of available iodine if associated with inherited defects in iodine utilization may contribute to the incidence of congenital deafness".

Gregg notes that the affected children in his series of cases had "widespread geographical incidence", and with this "suggested that there was some common factor in the production of the diseased condition", and that the defect, namely, affection of the heart, "was the result of some constitutional disturbance of toxic or infective nature rather than of a purely developmental defect". Can it be that iodine metabolism is concerned in these cases also—a point which does not appear to have been raised?

A further interesting fact is that both Gregg and Carruthers have noted that most of the babies were of "small size, ill-nourished and difficult to feed", though no direct statement has been made as to whether these babies could be considered cretins.

Does the virus of rubella disturb the iodine metabolism?

Yours, etc.,
W. R. F. FOX,
Squadron Leader, Royal
Undated. Australian Air Force.

COPIES OF JOURNALS AVAILABLE TO LIBRARIES.

SIR: The library of the Medical School of the University of Queensland has a collection of duplicate, and in some cases triplicate, copies of numbers of the following journals: *British Medical Journal*, THE MEDICAL JOURNAL OF AUSTRALIA, *The Australian and New Zealand Journal of Surgery, Surgery, Gynecology and Obstetrics, The British Journal of Surgery, Surgical Clinics of North America, The Journal of the Cancer Research Committee of the University of Sydney.*

Most of these numbers are now unobtainable, and would probably be of use in completing sets in other libraries.

Application for journals required should be made to this library, or a list could be furnished on request.

Yours, etc.,
E. S. MEYERS,
Dean, Faculty of Medicine.

The University of Queensland Medical School,
Herston Road,
Brisbane, N.1.
March 23, 1945.

SPRUE SYNDROME.

SIR: The case of "sprue syndrome" reported by Squadron Leader Isbister in the journal of April 14 is of considerable interest because the onset of the disease occurred while the patient was stationed at Cairns.

I have been out of touch with that part of Australia for so long that I do not know what is the position regarding the occurrence of sprue in this district in recent years, but I recollect that when I first visited Cairns (about 1910) an area at Babinda a few miles inland was regarded by the local practitioners as a sprue focus. Later (1920-1921), when I was associated with the late Dr. Breinl at Townsville, he told me he had collected a good deal of evidence that sprue was prone to occur along the course of the light railway from Cairns to Babinda.

Although it is now more or less agreed that sprue, when developed, is caused by deficiency or metabolic disturbance, the report of this case lends support to the view that there is a predisposing infectious or other factor which is the activator.

Yours, etc.,

Lachlan Park Hospital, New Norfolk, Tasmania. April 17, 1945.

PHILIP A. MAPLESTONE.

Naval, Military and Air Force.

CASUALTIES.

ACCORDING to the casualty list received on May 3, 1945, Lieutenant Colonel A. H. Powell, A.A.M.C., Armidale, New South Wales, is reported to have been placed on the "seriously ill" list.

Nominations and Elections.

THE following have applied for election as members of the New South Wales Branch of the British Medical Association:

Conlon, Leonard Telford, M.B., B.S., 1938 (Univ. Sydney), Flight-Lieutenant, 4, Rose Crescent, Mosman.

Snape, Margaret, M.B., B.S., 1944 (Univ. Sydney), Saint George District Hospital, Kogarah.

Medical Appointments.

Dr. Alan Lee, Dr. Konrad Hirchfeld, Dr. Lachlan Martin McKillop, Dr. Abraham Fryberg and Dr. Edward Holbrook Derrick have been appointed members of the Queensland Health Education Council in pursuance of provisions of *The Health Acts*, 1937 *to* 1945.

Obituary.

HUGH NOEL PUCKLE.

WE regret to announce the death of Dr. Hugh Noel Puckle, of Melbourne, which occurred on May 3, 1945, at Hobart.

Books Received.

"Textbook of Anæsthetics", by R. J. Minnitt, M.D. (Liverpool), D.A. (R.C.P. and S.Eng.), and John Gillies, M.C., M.B., Ch.B. (Edinburgh), D.A. (R.C.P. and S.Eng), with a chapter on Local and Regional Analgesia by L. B. Wevill, M.B., F.R.C.S.(Ed.); Sixth Edition; 1944. Edinburgh: E. and S. Livingstone Limited. 8½" × 5½", pp. 496, with 199 illustrations. Price: 25s. net.

"Manual of Public Health Hygiene", by J. R. Currie, M.A. (Oxon.), M.D., LL.D. (Glasgow), D.P.H. (Birmingham), F.R.C.P. (Edinburgh), and A. G. Mearns, B.Sc., M.D., B.Sc. (Public Health), D.P.H. (Glasgow), F.R.S. (Edinburgh); Second Edition; 1945. Edinburgh: E. and S. Livingstone Limited. 8½" × 5½", pp. 448, with 89 illustrations. Price: 21s. net.

Diary for the Month.

MAY 14.—Victorian Branch, B.M.A.: Hospital Subcommittee.
MAY 14.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
MAY 15.—Victorian Branch, B.M.A.: Organization Subcommittee.
MAY 15.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 16.—Western Australian Branch, B.M.A.: General Meeting.
MAY 17.—Victorian Branch, B.M.A.: Executive Meeting.
MAY 17.—South Australian Branch, B.M.A.: Council Meeting.
MAY 22.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 23.—Victorian Branch, B.M.A.: Council Meeting.
MAY 24.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 25.—Queensland Branch, B.M.A.: Council Meeting.
MAY 31.—New South Wales Branch, B.M.A.: Branch Meeting.
MAY 31.—South Australian Branch, B.M.A.: Scientific Meeting.
JUNE 1.—Queensland Branch, B.M.A.: Branch Meeting (Joseph Bancroft Memorial Lecture).
JUNE 5.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JUNE 6.—Victorian Branch, B.M.A.: Branch Meeting.
JUNE 6.—Western Australian Branch, B.M.A.: Council Meeting.
JUNE 7.—South Australian Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia. All Public Health Department appointments.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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